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VOLUME 7, NUMBER 1

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GASTROENTEROLOGY

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TABLE OF CONTENTS

Results of Hepatic Tests in Chronic Hepatitis Without Jaundice. JOHN R. NEEFE, M.D.	1
A Study of the Time of "Healing" of Peptic Ulcer in a Series of Sixty-Nine Cases of Duodenal and Gastric Craters. GEORGE M. CUMMINS, JR., M.D., M. I. GROSSMAN, PH.D., M.D., AND A. C. IVY, PH.D., M.D.	20
Nocturnal Gastric Secretion—Part II. Studies on Normal Subjects and Patients with Duodenal Ulcer. DAVID J. SANDWEISS, M.D., M. H. F. FRIEDMAN, PH.D., M. H. SUGARMAN, M.D., AND H. M. PODOLSKY, M.D.	38
Complications of Chronic Non-Specific Ulcerative Colitis. WILLIAM E. RICKETTS, M.D., AND WALTER LINCOLN PALMER, M.D.	55
The Etiology of Ulcerative Colitis: An Analytical Review of the Literature R. S. GINSBERG, M.S., M.D., AND A. C. IVY, PH.D., M.D.	67
Some Results of the Gastric Secretory Response of Patients Having Duodenal Ulcer Noted During the Administration of Benadryl ROBERT U. MOERSCH, M.D., ANDREW B. RIVERS, M.D., AND CARL G. MORLOCK, M.D.	91
Clinical Observations on the Use of Benadryl: Its Effect on Histamine-Induced Gastric Acidity in Man. THOMAS W. McELIN, M.D., AND BAYARD T. HORTON, M.D.	100
Separation and Assay of Secretin and Cholecystokinin. HENRY DOUBILET, M.D., M.S., F.A.C.S.	108
Clinical Pathological Conferences	118

EDITORIALS

FRANK HOWARD LAHEY, The Friedenwald Medalist for 1946	131
FRANK HOWARD LAHEY. A.C.I.	133

COMMENT

Histamine and Gastric Secretion in Relation to Anti-histamine Drugs M. I. G. AND A. C. I.	134
Observations on the Healing of Gastric Ulcers H. M. POLLARD, WILLIAM H. BACHRACH, AND MALCOLM BLOCK	136

BOOK REVIEWS

Alteracoes Hepaticas Na Tireotoxicose	139
Ambulatory Proctology	139

ABSTRACTS

140

For Instructions to Authors and the address of the Editor see the advertising section following the Abstracts.

VOLUME 7, NUMBER 1

GASTROENTEROLOGY

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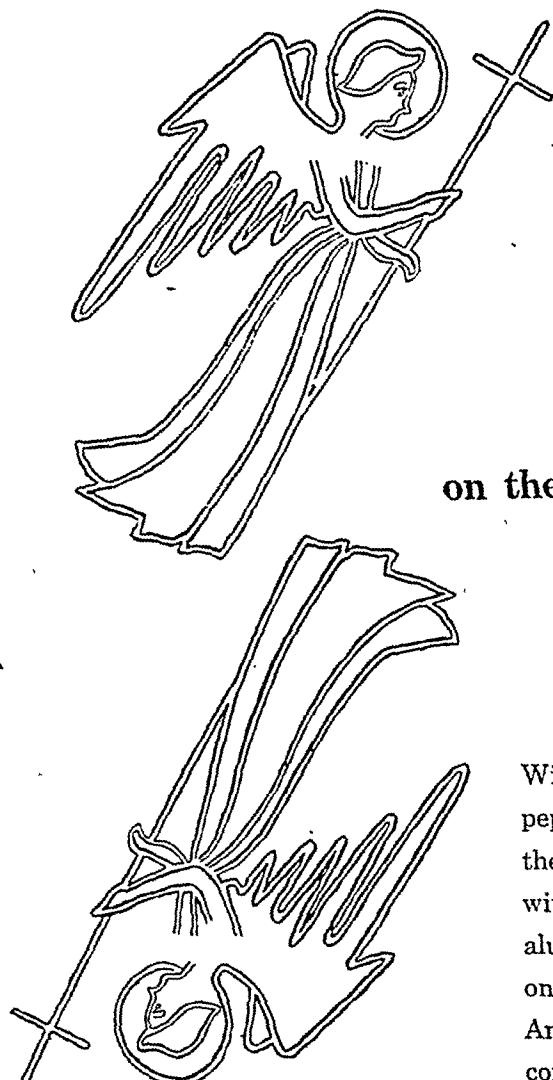
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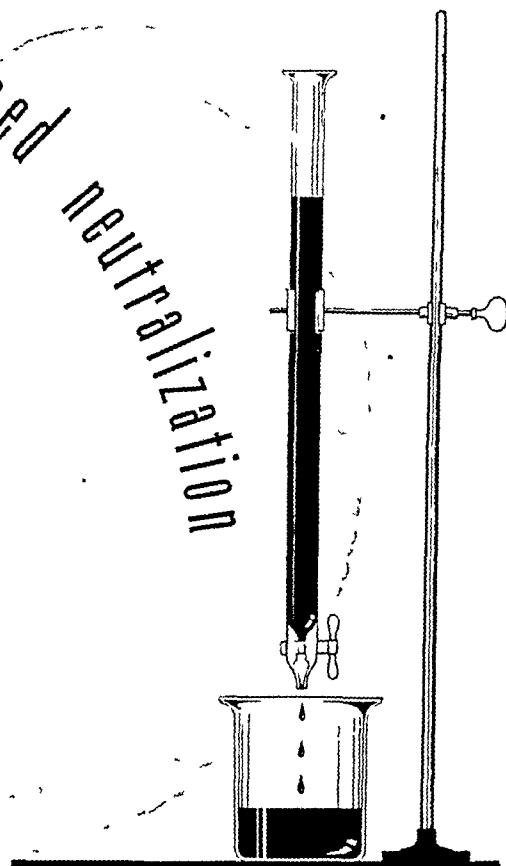
1. Lehr, D.: Proc. Soc. Exper. Biol. & Med. 58:11, 1945.

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GASTROENTEROLOGY

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VOLUME 7

July 1946

NUMBER 1

RESULTS OF HEPATIC TESTS IN CHRONIC HEPATITIS WITHOUT JAUNDICE

CORRELATION WITH THE CLINICAL COURSE AND LIVER BIOPSY FINDINGS¹

JOHN R. NEEFE, M.D.

From the Hospital of the University of Pennsylvania, Departments of Pediatrics and Medicine of the Medical School of the University of Pennsylvania

INTRODUCTION

Recent reports (1) have shown that acute infectious hepatitis and homologous serum hepatitis may be followed, in some instances, by a prolonged period of disability with or without other evidence of persistent hepatic disturbance. Barker, Capps, and Allen (1) have applied the term "chronic hepatitis"² to cases in which clinical manifestations or laboratory evidence of active hepatitis persisted for 4 months or more after the onset. Based on this arbitrary criterion, they reported that 18% of 431 unselected cases of infectious hepatitis observed in the Mediterranean Theatre of Operations were classified as "chronic hepatitis". Those persons who continue to have persistent clinical manifestations and disability following acute hepatitis but have no jaundice and little or no laboratory evidence of hepatic disturbance present a difficult problem in diagnosis, management, and disposition. Lack of definite evidence of hepatic or other organic disturbance, non-specific symptoms, and the frequent existence of a basis for functional or psychosomatic manifestations contribute to the diagnostic difficulties in these patients. During the past year, studies of infectious hepatitis induced in human volunteers have provided an opportunity to conduct serial studies of hepatic function over periods of 7 to 13 months on 4 such cases. The importance of this problem is indicated by the fact that 3 of these cases represented approximately 10% of the volunteers who developed infectious hepatitis as a result of inoculation with a hepatitis virus that had been responsible for an epidemic in a summer camp (2). In these cases, a diagnosis of chronic hepatitis without jaundice was made on the basis of the history, symptoms, laboratory evidence of hepatic

¹This investigation was conducted under the Commission on Measles and Mumps, Army Epidemiological Board, Preventive Medicine Service, Office of the Surgeon General, U. S. Army, Washington, D. C.

²The term "chronic", as used by Barker et al (and in the present report), refers "only to duration without implication regarding the nature of the pathologic process or the eventual prognosis."

disturbance, and, in 2 of the cases, on the microscopic findings in liver biopsy specimens. At certain stages of the disease in all of these cases, the serum thymol³ and colloidal gold tests furnished evidence of persistent hepatic disturbance that was not revealed by other hepatic tests (including the cephalin cholesterol flocculation test). As the responses of the thymol and colloidal gold tests in various conditions affecting the liver have not yet been clearly defined and because the present study apparently provides the first evidence that they may be of particular value in the diagnosis of this type of chronic hepatitis, the results of these studies appear to be of sufficient clinical importance to warrant a report at this time.

CASE ABSTRACTS

As this report is concerned primarily with the results of the laboratory studies, only abstracts of the case histories are presented. Other aspects of the problem of chronic hepatitis will be the subject of a future report.

Case 1: This volunteer, aged 23, developed acute hepatitis 24 days after ingesting a feces preparation known to contain a causative agent of infectious (epidemic) hepatitis (3). He developed overt jaundice during the acute phase, the serum bilirubin rising to a maximum concentration of 10.8 mgm./100 ml. The concentration of serum bilirubin returned to normal by the 58th day after the onset and other tests indicated progressively improving hepatic function. At approximately the same time that the serum bilirubin concentration returned to normal, a non-icteric relapse began. This was characterized clinically by the reappearance of lassitude, weakness, easy fatigue, periodic anorexia and nausea, and intermittent discomfort in the hepatic area. With complete bed rest, these symptoms soon disappeared although laboratory evidence of hepatic disturbance persisted. At first any physical activity resulted in reappearance of the symptoms, but as the months passed, the tolerance to physical activity gradually increased and the degree of hepatic disturbance indicated by liver function tests gradually decreased. Nine months after the onset, a liver biopsy was obtained.⁴ At the time of the operation, the liver was grossly normal in size and appearance. On microscopic examination of the specimen, the parenchyma appeared normal but the stroma of many of the portal triads was infiltrated with an excess of lymphocytes, plasma cells and histiocytes. These findings were interpreted by Lt. Colonel Balduin Lucké of the Army Institute of Pathology, Washington, D. C., as evidence of subsiding hepatitis. Lt. Colonel Tracy Mallory concurred in the opinion expressed by Lt. Colonel Lucké. Dr. Robert C. Horn, surgical pathologist at the Hospital of the University Hospital, also examined a portion of the same liver biopsy independently. The same microscopic findings were reported and were interpreted by him as follows: "This biopsy

³ The term "thymol test" is used herein to indicate the combined thymol turbidity and thymol flocculation tests (see methods).

⁴ The liver biopsies were performed by Dr. Jonathan Rhoads and Dr. C. Everett Koop, both of the Department of Surgery, Hospital and School of Medicine of the University of Pennsylvania.

shows evidences of active disease which is neither acute or destructive but rather is a late or chronic stage." From the 10th to the 12th months after the onset, moderate physical activity still resulted in undue fatigue, mild anorexia, and vague discomfort in the hepatic area to the extent that he voluntarily restricted ordinary physical activities. After the 12th month, no objective evidences of persistent hepatitis could be detected and restriction of physical activity was no longer necessary. At the time of writing (13th month), he still reported transient fatigue and vague discomfort in the hepatic area after strenuous physical exertion. As no objective evidences of persistent hepatic or other organic disturbance could be detected and routine physical activity was well tolerated, it appeared that complete, or nearly complete, recovery from the chronic hepatitis had occurred.

Case 2: Thirty-two days after ingesting the feces preparation known to contain the causative agent of infectious (epidemic) hepatitis, this volunteer, aged 21, developed acute hepatitis. Overt jaundice never was apparent although subclinical jaundice (maximum total serum bilirubin concentration—1.9 mgm./100 ml.) was present between the 10th and 19th days of the disease. The acute phase of the disease was relatively mild and, except for minimal laboratory evidence of persistent hepatic disturbance, he appeared to have recovered completely within 4 weeks of the onset. After being asymptomatic for approximately 2 months, including 1 month of relatively normal physical activity, a non-icteric relapse began. This was characterized by weakness, easy fatigue, "nervousness," mild anorexia, and mild discomfort in the hepatic area. The symptoms were promptly relieved by bed rest but reappeared with attempts to resume physical activity. The symptoms and course were similar to those of case 1, the course being marked by a very slow but gradual increase in the tolerance to physical activity. A liver biopsy was performed 6 months after the onset of acute hepatitis (3 months after the onset of the relapse). At operation, the liver was grossly normal in size and appearance. On microscopic examination of the liver specimen, the stroma of most of the portal triads contained a moderate excess of cells, mostly lymphocytes and histiocytes. In the interior of some lobules, minute foci of cell reaction similar to those in the portal triads were observed. Some of the liver cells were swollen and binucleated, their appearance resembling that of regenerated liver cells. The microscopic findings were interpreted by Lt. Colonel Lucké as evidence of subsiding hepatitis, the process being somewhat more active than that observed in the specimen from case 1. From the 6th to the 9th months following the onset of acute hepatitis, mild physical exertion still resulted in undue fatigue and "nervousness" and prevented satisfactory performance of routine duties. After the 10th month, no objective evidences of persistent hepatitis could be detected, physical activity was well tolerated and clinical recovery apparently was complete.

Case 3: Twenty-one days after the ingestion of the feces preparation containing the causative agent of infectious (epidemic) hepatitis, this volunteer, aged 24, developed acute hepatitis. Overt jaundice was present during the acute phase of the disease, the serum bilirubin concentration rising to a maximum of 10.6 mgm./100 ml. The serum bilirubin concentration returned to normal by the 56th day after the onset.

Although other tests at this time indicated persistent hepatic dysfunction, he was free from symptoms and showed no ill effects from gradual resumption of activity. However, after approximately 6 weeks of relatively normal activity without symptoms, and during which time the liver function tests showed a gradual decrease in the degree of hepatic disturbance, he began to have symptoms of easy fatigue, mild anorexia, lassitude, and slight discomfort in the hepatic area. This relapse, which began approximately 2 months after the disappearance of jaundice, responded very slowly to treatment. During the 7th and 8th months after the onset of the acute disease, the symptoms still persisted in spite of continued complete restriction of activity. Abdominal examination revealed no significant findings. At the time of writing (9th month), he noted a definite improvement in his subjective symptoms although lassitude and easy fatigue with mild exertion continued.

METHODS

The hepatic tests employed in the study of these cases are listed below. The criteria for normal and abnormal responses listed for each of these procedures are based on the results obtained from tests on multiple sera from each of 50 or more apparently normal persons without history, physical findings, or other evidence of hepatic disease. These observations will be described in more detail in a subsequent publication (4c).

(a) *The total serum bilirubin concentration* was determined by the method of Malloy and Evelyn (5), using American bilirubin preparations (Eastman and Pfahnestiehl) for calibration of the photoelectric colorimeter. Values exceeding 1.4 mgm./100 ml. were regarded as abnormal (4). (b) *The prompt direct-reacting serum bilirubin concentration* was estimated by the method of Malloy and Evelyn (5), using the 1 minute reading advocated by Ducci and Watson (6). Values exceeding 0.21 mgm./100ml. were considered abnormal (4c). (c) The Godfried modifications of the Harrison and diazo spot tests (7) were used for the detection of *urine bilirubin*. Results were graded from negative (-) to 4+ and readings of 1+ or greater were regarded as abnormal. Plus-minus (\pm) readings (weak atypical color reactions) were not considered significant as they have been observed frequently with urines from apparently normal persons (4c). (d) *Urine urobilinogen* was determined by the simplified quantitative method of Watson, Schwartz, Sborov, and Bertie (8) and also by the method of Wallace and Diamond (9). The tests were preformed on 2 hour specimens collected between 6:30 and 8:30 A.M. and between 12 noon and 2 P.M. Two specimens were obtained as the urobilinogen content of urine apparently varies at different times of the day, pathologic urobilinogenuria occasionally being found only in afternoon specimens (8). For this reason Watson et al. have recommended the use of specimens collected between 2 and 4 P.M. However, because of the large number of specimens examined daily during these investigations, it was technically inconvenient to use specimens which were not available until 4:00 P.M. With the Watson procedure, values exceeding 1.4 E.U. in the morning specimens and 2.4 E.U. in the afternoon specimens (12 noon to 2:00 P.M.) were regarded as abnormal (4c). With

the Wallace and Diamond test, positive reactions with urine dilutions of 1:30 or greater were regarded as abnormal (4). (e) *The bromsulphalein test* consisted of photoelectric measurement on the amount of dye remaining in the serum 45 minutes after the intravenous injection of 5 mgm. of bromsulphalein per kilogram of body weight. The photoelectric measurement was made by the technique described in the brochure of the Photovolt Corporation (New York). The mean retention for 155 tests on 72 apparently normal persons was 1.4%, the normal range varying between 0 and 6% (4c). (f) *The intravenous hippuric acid test* was performed in accordance with the technique of Quick (10). The results were expressed in grams of benzoic acid excreted as hippuric acid in the urine in 1 hour. Values less than 0.65 grams were considered abnormal (4). (g) *Serum total protein, albumin, and globulin concentrations* were determined by the photoelectric method of Kingsley (11). The normal ranges were found to be as follows (4): Total protein—6.0 to 8.3 grams/100 ml.; albumin—4.0 to 5.8 grams/100 ml.; globulin—1.3 to 2.7 grams/100 ml. (h) *Serum alkaline phosphatase activity* was estimated by the method of Bodansky (12). The normal range was found to be 1 to 4 Bodansky units (4). (i) *Total and esterified serum cholesterol* were determined by the method of Reinhold (13). The normal ranges were (4): Total cholesterol—110 to 280 mgm./100 ml.; cholesterol esters—47 to 75% of the total cholesterol. (j) *The cephalin cholesterol flocculation test* was performed by the technique of Hanger (14) as modified by Neefe and Reinhold (15). The Difco cephalin cholesterol reagent was used. Flocculation was graded from 0 to 4+ and the 48 hour reading is reported herein. Tests graded 2+ or greater were considered abnormal (4a, 4c). (k) *The serum colloidal gold test* was performed according to the modified technique of MacLagan (16). A colloidal gold sol prepared and standardized in the laboratory of Dr. Fred Boerner, Graduate Hospital of the University of Pennsylvania, according to the technique of Kolmer and Boerner (17), was employed. In order to simplify comparison with the results of the cephalin cholesterol and thymol flocculation tests, the results of the colloidal gold tests also were graded from 0 to 4+ rather than 0 to 5+ as recommended by MacLagan. On the basis of the results of 986 tests on 168 persons without clinical or laboratory evidence of hepatic disease, readings greater than 1+ were regarded as abnormal (4c). (l) The *thymol test* was performed in conformance with the technique recommended by MacLagan (18), but included readings of the degree of flocculation after 18 hours (thymol flocculation test) in addition to the recommended 30 minute turbidity reading (thymol turbidity test). The saturated thymol buffer was prepared according to MacLagan's directions. As the pH obtained on thymol buffers so prepared sometimes varied, it was adjusted to the pH recommended by MacLagan whenever necessary. The turbidity of the thymol serum mixtures was compared with the turbidity of the Kingsbury-Clarke protein standards.⁵

Thymol turbidities of 3.0 or more units at 30 minutes were considered abnormal on the basis of (4c): (a) 332 tests on 32 apparently normal male volunteers and (b) 118 tests on 87 hospital and O.P.D. patients without clinical or laboratory manifestations of hepatic disease. The range of turbidities obtained with this series of ap-

⁵ Prepared by the Hartman-Leddon Company, Philadelphia, Pa.

parently normal sera (0 to 2.5 units) thus was smaller than that reported by MacLAGAN (18) and by WATSON et al. (0 to 4 units) (19).

The *thymol flocculation test*, as referred to herein, merely represents a reading of the degree of flocculation occurring after approximately 18 hours in the thymol-serum mixtures used for the 30 minute turbidity reading. During this period, the mixtures were permitted to stand at room temperature in subdued light. The degree of flocculation was graded from 0 to 4+, using the same criteria as those employed in reading the cephalin cholesterol flocculation test. Although the thymol flocculation test was somewhat more difficult to grade than the cephalin cholesterol flocculation test, comparable readings were obtainable by different observers. Flocculation greater than 1+ was regarded as abnormal on the basis of the results obtained on the same number of tests on the same sera that were used for evaluation of the thymol turbidity test.

(m) *Sedimentation rates* were determined by the Wintrobe technique (20). Rates exceeding 12 mm. per hour in males and 20 mm. per hour in females were considered abnormal.

RESULTS

Most of the liver function tests described under "Methods" were performed on the volunteers one or more times weekly both before and after the onset of hepatitis. The observations have extended to date over periods of 13, 10, and 9 months after the onset of acute hepatitis in cases 1, 2, and 3, respectively. As space does not permit the inclusion of all the laboratory data, only the results obtained with the different tests at approximate monthly intervals after the onset of hepatitis are presented in tables 1 to 3 inclusive. Representative results of the tests performed prior to the inoculation of the subjects with hepatitis virus also have been included in the tables to assist in the evaluation of the results obtained at various intervals after the onset of hepatitis. Also presented in the tables are the results obtained on a patient (case 4) studied only during the 6th and 7th months of her illness (see discussion).

Table 1 shows that the *total serum bilirubin concentration* was not significantly elevated in any of the 3 experimental cases after the second month of the disease. The *prompt direct-reacting serum bilirubin concentration* was not significantly increased in any of the 3 cases after the first month. None of the 3 cases showed *bilirubinuria* after the second month and consistent increases in *urine urobilinogen* were not detected after the second month. Abnormal retention of *bromsulphalein* was not found after the 5th month in any of the 3 cases. *Sedimentation rates* were found to be somewhat irregular, but, in general, were significantly elevated until the end of the 6th month in cases 1 and 2 and to the time of writing (9th month) in case 3. Although not specifically a test of liver function and subject to influence by a variety of incidental conditions, the results of this test in these cases seemed worthy of inclusion.

TABLE 1

Results of total serum bilirubin, prompt direct-reacting serum bilirubin, urine bilirubin, urine urobilinogen, bromsulphalein, and sedimentation rate determinations obtained at monthly intervals on 4 persons with chronic hepatitis following an attack of acute infectious hepatitis. Liver biopsies obtained during the 9th month from case 1 and during the 6th month from case 2 showed evidence of persistent mild hepatitis. As case 4 was observed only during the 6th and 7th months of her illness, only the laboratory data obtained during that period are available. The normal range of results for the individual tests is given below the name of the procedure in the first column (see methods). The results given for cases 1, 2, and 3 in the second column ("Before onset") are representative of those obtained on these persons before their inoculation with the hepatitis virus. The urine urobilinogen results reported in the table as increased (I) or normal (N) are based on the results obtained by both the Watson and the Wallace and Diamond methods. The results on Case 3 for the 10th month, obtained after submission of the manuscript for publication, have been added to the tables but are not discussed in the text.

TEST AND NORMAL RANGE (SEE LEGEND)	BEFORE ON- SET N S	MONTHS AFTER ONSET OF HEPATITIS														
		3	1	2	3	4	5	6	7	8	9	10	11	12	13	
Total serum bilirubin 0.1 to 1.4	1	0.9	10.5	2.4	1.5	0.9	0.5	0.7	0.5	0.6	0.8	0.6	0.6	0.7	0.7	0.9
	2	1.0	1.9	0.5		0.5	0.5	1.1	0.9	0.5	0.5	1.1	0.6			
	3	0.7	10.6	1.9	1.4	0.8	0.8	1.0	0.5	0.5	0.8	0.7	0.4			
	4							0.6	0.4							
Prompt direct-reacting serum bilirubin 0 to .21	1	.05	3.8	.65	.10	.20	.20	.10	.10	.10	.10	.05	.10	.05	.05	.10
	2	.10	.25	.05				.05	.05	.05	.10	.15	.10			
	3	.20	6.80	.35	.15	.18	.10	.08	.10	.10	.10	.10	.08			
	4							.05	.10							
Urine bilirubin (- to ±)	1	—	4+	2+	1+	±	—	—	—	—	—	—	—	—	—	—
	2	—	2+	—	—	—	—	—	—	—	—	—	—	—	—	—
	3	—	4+	±	±	±	—	—	—	—	—	—	—	—	—	—
	4															
Urine urobilinogen	1	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	2	N	I	N		N	N	N	N	N	N	N	N	N	N	N
	3	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	4															
Bromsulphalein retention 0 to 6%	1	5	42	1	10	19	17	12	4	3	3	4	3	3	3	2
	2	0					5	3	3	3	3	4	3	2		
	3	2		12	9	8	5	6	6	2	4	3	3	3		
	4															
Sedimentation rate 0 to 12	1	10	25	23	8	15	18	16	14	9	10	13	8	7	10	8
	2	12	15	13				11	31	10	11	8	9			
	3		32	16	23		22	19	34	33	21	18				
	4							14								

Table 2 shows that the *total serum cholesterol concentration* did not show sufficient variation from the normal range in any of these cases to be of diagnostic value at any time. The serial studies showed significant changes during the

course of the disease in the individual cases but single determinations provided little or no information of positive value. Abnormal values for *esterified serum cholesterol* were not found in any of the 3 cases after the 1st month. Determinations of *alkaline phosphatase activity* in these cases were too infrequent to warrant conclusions. However, experience with other cases (5) and the scattered results on the present cases suggest that this procedure has little value in the diagnosis of this type of hepatitis. The *intravenous hippuric acid* test likewise was not helpful in these cases.

TABLE 2

Results of total and esterified serum cholesterol, serum alkaline phosphatase, and intravenous hippuric acid tests on 4 persons with chronic hepatitis following an attack of acute infectious hepatitis. For other details refer to legend of table 1.

TEST AND NORMAL RANGE	CASE	BE-FOR E ONSET	MONTHS AFTER ONSET OF HEPATITIS											
			.5	1	2	3	4	5	6	7	8	9	10	
Total serum cholesterol 110 to 300	1	172	232	316	166	148	206	194		194		166	188	178
	2	186	244	206				180	176	190	194	178	186	
	3	204	110	210	204	182	176	166	178	152		232		
	4								274	212				
Esterified serum cholesterol % of total 47 to 80	1	62	23	46	61	57	63	56		64		78	62	61
	2	54	15	49				60	49	61	55	57	58	
	3	50	9	43	50	52	56	49	59	64		48		
	4								52	43				
Alkaline phosphatase 0.9 to 4.0	1	3.8										2.4	2.1	
	2								0.9	1.6		1.8	1.4	
	3					1.9		1.5		2.3				
	4							1.4	2.4					
Hippuric acid excretion 0.65 to 1.0	1	.88				.9							.8	
	2	.85	1.0						1.0			.9		
	3								.70					
	4									.85				

Table 3 shows that the *cephalin cholesterol flocculation test* was not consistently positive in Case 1 after the 4th month and in Case 2 after the 6th month. In Case 3, it remained strongly positive until the end of the 8th month. At the time of writing (9th month), however, the reaction (1+) was no longer significantly positive. The *colloidal gold test* continued to be significantly positive in Case 1 until the end of the 8th month and in Case 2 until the end of the 9th month. In Case 3, the colloidal gold test still was strongly positive at the time of writing (9th month). The *thymol turbidity test* was significantly positive in Case 1 until the end of the 7th month, in

Case 2 until the end of the 8th month. In Case 3, it remained significantly positive until the end of the 8th month but at the time of writing (9th month), the turbidity reading was no longer significantly positive. The *thymol flocculation test* continued to be significantly positive in Case 1 until the end of

TABLE 3

Results of the cephalin cholesterol flocculation, colloidal gold, thymol turbidity, thymol flocculation, serum globulin and serum albumin determinations obtained at monthly intervals on 4 persons (cases 1, 2, 3 and 4) with chronic hepatitis following an attack of acute infectious hepatitis. For other details refer to legend of table 1.

TEST AND NORMAL RANGE	CASE	BEFORE ONSET	MONTHS AFTER ONSET OF HEPATITIS													
			3	1	2	3	4	5	6	7	8	9	10	11	12	13
Cephalin cholesterol flocculation 0 to 1+	1	0	4+	1+	2+	4+	4+	0	0	0	±	1+	0	1+	0	0
	2	0	4+	4+	0	0	1+	4+	2+	0	0	0	0	0	0	0
	3	0	4+	4+	4+	4+	2+	3+	3+	3+	3+	1+	0			
	4								± 0							
Colloidal gold 0 to 1+	1	0	4+	±	1+	4+	4+	4+	3+	3+	2+	0	1+	0	0	0
	2	0	3+	4+	±	±	4+	4+	4+	3+	2+	2+	0			
	3	0	4+	4+	4+	3+	3+	4+	4+	4+	4+	4+	3+	3+		
	4									4+ 3+						
Thymol turbidity 0 to 3.0	1						6.0	7.5	7.5	2.5	4.0	2.5	2.0	2.0	3.0	2.0 1.5
	2	1.1	7.0	7.5	3.5	5.0	8.0	9.0	7.0	4.0	3.5	3.0	2.0			
	3	1.5	15.0	7.5	5.0	4.8	5.5	6.0	6.0	6.0	7.0	3.0	3.0			
	4									5.0 6.5						
Thymol flocculation 0 to 1+	1						3+	4+	4+	3+	2+	2+	2+	2+	3+	1+ ±
	2	0	3+	4+	1+	3+	4+	3+	4+	3+	3+	2+	±			
	3	0	4+	4+	3+	3+	3+	4+	3+	4+	3+	4+	3+			
	4									4+ 3+						
Serum globulin 1.3 to 2.7	1	2.5	3.3	2.9	2.9	3.0	3.1	3.1		2.4	2.4		2.4	2.2	2.4	2.5
	2	1.9	2.9	2.5					3.2	2.7		2.0	2.2	1.8		
	3	1.8	3.0	3.6	3.2	2.2	3.0	3.2	3.2	2.4	0.3	3.6	3.0	2.7		
	4									2.4	2.4					
Serum albumin 4.0 to 5.8	1	4.9	4.2	4.8	5.0	4.9	5.2	5.0		5.1	5.3		5.0	4.9	4.8	4.8
	2	5.3	5.0	5.5					5.4	5.3		5.4	5.5	5.3		
	3	5.1	4.7	5.3	5.3	4.7	5.1	5.1	4.7	4.4	5.2	5.3	5.5			
	4									5.1	5.3					

the 11th month, in Case 2 until the end of the 9th month. In Case 3, it remained strongly positive at the time of writing (9th month). The concentration of *serum globulin* was elevated in Cases 1 and 2 until the end of the 6th month and still was elevated in Case 3 at the time of writing (9th month). Although decreases in the concentration of *serum albumin* occurred in the indi-

vidual cases during the early acute stage of the disease, the values were within the normal range for the method used in all 3 cases after the 2nd month of the disease.

It is of particular interest to note the results of the various tests on Cases 1 and 2 at the time of liver biopsy. In respect to Case 1, the only test giving a significantly-positive result at the time of liver biopsy (9th month) was the thymol flocculation test. In view of the fact that symptoms, disability, and microscopic evidence of mild hepatitis were present at that time, it is reasonable to assume that the positive thymol flocculation test was a manifestation of the hepatic disturbance. Furthermore, the thymol flocculation test was the only test that remained consistently positive in this case until clinical recovery was nearly complete (12th month), the results thus paralleling the clinical course more closely than any of the other tests employed. In respect to Case 2, the only tests giving significantly positive results at the time of liver biopsy (6th month) were the cephalin cholesterol flocculation, colloidal gold, thymol turbidity, and thymol flocculation tests. The cephalin cholesterol flocculation test alone would have been of questionable significance as 2+ reactions occasionally are obtained with sera from apparently normal persons and the reliability of the test is dependent on a variety of technical factors. The strongly positive collodial gold, thymol turbidity, and thymol flocculation tests thus provided important additional evidence of the persistent hepatic disturbance in this case. Although mild symptoms and limited tolerance to physical activity persisted to the 10th month, the cephalin flocculation test gave negative results after the 7th month. The thymol and colloidal gold tests, on the other hand, gave positive results up to the 10th month at which time clinical recovery was nearly complete.

DISCUSSION

The 3 cases described above provide experimental evidence that non-icteric hepatitis associated with incapacitating symptoms may persist, in some cases, for months after the evidences of acute infectious hepatitis have subsided. In this respect, case 2 warrants special comment. Under other circumstances, it is quite possible that the illness of this volunteer would not have been recognized as hepatitis. During the acute phase of the disease, the symptoms were relatively mild and non-specific, overt jaundice never was apparent, and clinical recovery appeared to be complete. If this phase of the illness had been encountered in ordinary practice, this patient probably would not have been hospitalized or subjected to special diagnostic tests as the clinical picture was similar to that commonly diagnosed as "grippe", "intestinal flu", or "gastroenteritis." Thus the relationship of his non-icteric relapse, occurring after an asymptomatic interval and resulting in partial disability

for months, easily might have been overlooked, especially if the earlier acute phase of the illness had not been recognized as acute hepatitis. The difficulty in diagnosis of the cause of the symptoms associated with his non-icteric relapse was increased further by the fact that cephalin cholesterol flocculation test was the only test, other than the colloidal gold and thymol tests, suggesting the presence of hepatic disturbance. The positive cephalin cholesterol flocculation test alone would not have been sufficient to warrant a diagnosis of hepatitis and subsequently, in spite of continued symptoms and biopsy evidence of hepatitis, this test gave negative results.

It is apparent that the diagnosis of chronic hepatitis may be extremely difficult and it seems probable that many cases have escaped recognition in the past. In the present cases, the biopsy findings, the close correlation between the clinical course and the results of the thymol and colloidal gold tests, the consistency of the findings in all 3 cases, and the absence of any other explanation provide strong evidence that the positive thymol and colloidal gold tests were manifestations of the persistent hepatitis. For this reason, the results of the present study showing that, in certain stages of chronic non-icteric hepatitis, the thymol and colloidal gold tests may furnish evidence of persistent hepatic disturbance that is not revealed by other hepatic tests appear to be of considerable clinical importance.

To further illustrate the usefulness of the thymol and colloidal gold tests in the diagnosis of chronic hepatitis without jaundice and also to show that their value is not confined to experimentally induced hepatitis, it has seemed desirable to include at this point the following abstract of a case recently observed at the Hospital of the University of Pennsylvania:

The patient was a white woman, aged 27, who had been admitted in January, 1945 to an Army Hospital in Italy where a diagnosis of acute infectious hepatitis with jaundice was made. Overt jaundice disappeared within a few weeks and she was started on a reconditioning program. Although she experienced easy fatigue, anorexia, nausea, and discomfort in the right upper quadrant during the reconditioning program, her jaundice did not recur and she was relatively free from symptoms after rest. She therefore was discharged from the hospital to return to her work with one of the Government special service units. During the next few months she failed to regain the weight lost during the acute hepatitis and she was readmitted to different army hospitals on several occasions because of recurrence of the symptoms cited above whenever she attempted any physical activity. She stated that she was subjected to repeated studies of liver function⁶ during her periods of hospitalization and was

⁶ It is reasonable to assume that these studies did not include the colloidal gold and thymol tests as the latter was first reported in November, 1944, and the former was not commonly employed in army hospitals.

told on each occasion that the tests revealed no evidence of hepatic disturbance. Because of her continued disability she was returned to her home and as her condition failed to improve after a period of rest and careful diet at home, she was admitted to the Hospital of the University of Pennsylvania for study in July, 1945, 7 months after the onset of the acute attack. On admission, her chief complaints consisted of: (1) pronounced weakness and easy fatigue, (2) periodic anorexia and nausea, (3) intermittent discomfort in the hepatic area, (4) failure to regain her normal weight. Most of these symptoms were minimal or absent when at rest in bed but reappeared promptly with any activity. She was considerably worried by the fact that no definite evidence of persistent hepatitis or other organic cause for her disability had been revealed by her previous studies and was further disturbed emotionally by the suspicion that others considered her symptoms to be of psychoneurotic origin. On examination, the edge of the liver seemed to be just palpable below the costal margin at maximum inspiration. There was slight sensitivity to deep palpation in this area but this was not greater than that occasionally observed in apparently normal persons. No other significant physical signs were detected. Hematologic studies gave the following results: (1) erythrocyte count—4 million/cu. mm.; hemoglobin—12.5 gms.; (2) leucocyte count—5500/cu. mm.; (3) differential leucocyte count—neutrophiles—57%; lymphocytes—39%; monocytes—4%. Blood smears for malaria were negative. The erythrocyte sedimentation was normal (6 mm./hr., Wintrobe). Routine examination of the urine revealed no abnormalities. The results of the hepatic studies were as follows: (1) total serum bilirubin—0.65 mgm./100 ml.; (2) prompt direct-reacting serum bilirubin—0.06 mgm./100 ml.; urine bilirubin—negative; urine urobilinogen—0.3 E.U.; bromsulphalein retention at 45 minutes—4%; total serum protein—7.5 gm./100 ml.; serum albumin—5.1 gm./100 ml.; serum globulin—2.4 gm./100 ml.; total serum cholesterol—274 mgm./100 ml.; esterified serum cholesterol—144 mgm./100 ml. (52% of total); prothrombin activity—75% of normal; alkaline phosphatase—1.4 Bodansky units; intravenous hippuric acid excretion—0.85 gm.; cephalin cholesterol flocculation test—negative; serum colloidal gold reaction—4+; thymol turbidity test—5.0 units; thymol flocculation test—4+. Repetition of the tests 1 month later yielded results almost identical with those cited.

The history, clinical manifestations, and the results of the studies on this case thus were similar to those of the 3 volunteers. Except for the thymol and colloidal gold tests, all of the hepatic tests were negative. This supported the patient's statement that her previous studies had revealed no evidence of hepatic disturbance. In view of the experience with chronic hepatitis in the volunteers, the history of acute hepatitis, and the absence of any other explanation, the positive thymol and colloidal gold tests appeared to provide an adequate basis for a diagnosis of chronic hepatitis in this case.

In his original description of the thymol turbidity test, MacLagan states (18), "When the test (thymol turbidity) is positive, flocculation frequently occurs on standing overnight, but this is not an essential part of the test." Observation for the occurrence of this flocculation and estimation of its degree (thymol flocculation test) were not recommended by MacLagan as part of the thymol turbidity test, and in the other reports on the test published to date (19, 21, 22) only the 30 minute turbidity has been discussed. The present study thus appears to be the first in which the thymol flocculation reaction has been used in the study of hepatic disease. The data show that the thymol flocculation test was strongly positive whenever the thymol turbidity test was positive. Of particular interest is the fact that the thymol flocculation test remained significantly positive in these cases for some time after the thymol turbidity had returned to within the normal range (3.0 units or less). That the positive thymol flocculation tests were of significance as evidence of persistent hepatic disturbance when the results of the thymol turbidity and other hepatic tests were within the normal range is indicated by the facts that: (1) the positive thymol flocculation tests were associated with clinical symptoms in all 3 cases; (2) in cases 1 and 2, the thymol flocculation test did not become negative until almost complete clinical recovery had occurred; (3) at the time the liver biopsy was obtained from case 1, the thymol flocculation test was the only one of the group of tests herein employed (including the thymol turbidity) that remained significantly positive, the biopsy showing definite evidence of mild hepatitis; (4) in addition to the correlation with continued symptoms in cases 2 and 3, positive colloidal gold tests supported the significance of the positive thymol flocculation tests that were obtained after the return of the thymol turbidity readings to the normal range. It appears, therefore, that in all of the present cases, the thymol flocculation test was a more sensitive indicator of the persistent hepatic disturbance than the thymol turbidity test. In these cases the colloidal gold test also appeared to be a somewhat more sensitive indicator of the persistent mild hepatic disturbance than the thymol turbidity test. However, the thymol flocculation test was equal, and in case 1 superior, to the colloidal gold test in sensitivity for this type of hepatic disturbance. Other studies (23) have shown that the thymol flocculation test may become positive in early acute hepatitis before the thymol turbidity and colloidal gold tests. The data thus suggest that the thymol flocculation test may be one of the most sensitive indicators of certain types of hepatic disturbance and indicate the desirability of including it routinely as part of the thymol turbidity test. In addition to supplementing and possibly increasing the sensitivity of the thymol turbidity test, the presence or absence of flocculation after 18 hours may aid in evaluating the significance of borderline or weakly positive thymol turbidity readings. Thus a turbidity of 3.0 to 5.0 units associated with 2 to 4+ flocculation at 18 hours is more apt to be significant than the same tur-

bidity reading with no flocculation at 18 hours. These observations do not decrease the value of the thymol turbidity test, which, when positive, affords a quantitative reading and also is more promptly available.

The liver biopsy findings in cases 1 and 2 suggest a possible explanation for the failure of many liver function tests to reveal the persistent hepatic disturbance in this type of chronic hepatitis. The polygonal cells of the liver showed no signs of degeneration or necrosis and no evidence suggestive of obstruction of the intrahepatic biliary passages was apparent. It is not surprising, therefore, that normal results were obtained with hepatic tests that depend chiefly on the state of the polygonal cells and the patency of the intrahepatic biliary passages. The only residual abnormality apparent in the biopsy specimen from case 1 was the cellular infiltration of the stroma of the portal triads. This also was an outstanding lesion in the biopsy specimen from case 2, which, in addition, showed small foci of cellular infiltration within the lobules. For this reason, it seems probable that the process causing the cellular infiltration also was responsible for the positive thymol and colloidal gold tests. In case 1, the cephalin cholesterol flocculation test had been negative during the 4 months prior to biopsy, and, in all of these cases, this test became negative before the thymol and colloidal gold tests. This also has been the usual sequence of events during recovery from ordinary acute infectious hepatitis as observed in volunteers (23, 24). This suggests that the cephalin cholesterol flocculation test either is less sensitive than the thymol and colloidal gold tests or that they depend on different types of hepatic involvement, the lesion responsible for the positive cephalin cholesterol flocculation tests in hepatitis subsiding before the lesion responsible for the positive thymol and colloidal gold tests. That the earlier return to normal of the cephalin cholesterol flocculation test probably is not due to relative insensitivity as compared with the thymol and colloidal gold tests is indicated by other studies (19, 23) which have shown that the cephalin cholesterol flocculation test may be strongly positive in certain types of hepatic disease in which the thymol and colloidal gold tests are negative. These observations provide considerable evidence that the type of hepatic disturbance producing positive cephalin cholesterol flocculation tests differs from that producing positive thymol and colloidal gold tests.⁷ On the basis of different results with the thymol turbidity and cephalin cholesterol flocculation tests on patients with hepatic disease other than hepatitis, Watson and Rappaport (19) also came to the conclusion that the mechanisms of the two tests were not identical. In patients with hepatitis, however, they found no significant disagreement be-

⁷ Recant, Chargaff and Hanger (Proc. Soc. Exp. Biol. and Med., 60: 245, 1945) recently have reported observations indicating fundamental differences in the mechanisms of the cephalin cholesterol flocculation and thymol turbidity tests.

tween the results of the two tests and stated that in hepatitis the trend of each test and the information gained were essentially the same. On the basis of their data, they expressed the opinion that, in respect to hepatitis, the thymol turbidity test is fully as useful and reliable as the cephalin cholesterol flocculation test once the disease is well established. The present data are in accord with this opinion. However, these and other data (23) indicate that in infectious hepatitis the thymol test usually is superior to the cephalin cholesterol flocculation test as an index of recovery from hepatitis. The superiority is more evident when the thymol flocculation test is used in conjunction with the turbidity test. Thus the thymol test (turbidity and/or flocculation) usually continues positive for a longer period of time during convalescence and correlates better with the disappearance of symptoms than the cephalin flocculation test. This apparent superiority of the thymol test during the later stages of hepatitis does not extend to the early or pre-icteric stages of the disease as recent data (23) on the responses of these tests during the first week of hepatitis indicate that the cephalin cholesterol flocculation test tends to become positive 1 to several days earlier than the thymol and colloidal gold tests. It thus appears that in hepatitis, the cephalin cholesterol and thymol tests may provide information concerning two different types of hepatic involvement both of which probably are present at certain stages of the disease but one of which may appear or disappear before the other. For these reasons, the use of both tests frequently provides more information than either one alone. Hanger feels that the positive cephalin cholesterol flocculation in humans is related chiefly to active injury of the hepatic polygonal cells. On the basis of the liver biopsy findings in cases 1 and 2, the positive thymol and colloidal gold tests apparently were related to the persistent inflammatory process which at that time did not seem to involve the polygonal cells. As polygonal cell injury undoubtedly was present earlier, the subsidence of this process and the persistence of the inflammatory process, noted particularly in the portal triads, appears to be a reasonable explanation for the persistence of positive thymol (turbidity and/or flocculation) and colloidal gold tests after the cephalin flocculation test had become negative. Such an explanation also could account for the varying results obtained in other types of hepatic disease, the response depending on the type or types of hepatic involvement present. For these reasons, the thymol and colloidal gold tests should not be regarded as substitutes for the cephalin cholesterol flocculation test or vice versa. As the response of each of these tests in relation to the others eventually may have diagnostic and prognostic significance, further studies of their responses in various types of hepatic disease and at different stages of the same disease are indicated.

It seems desirable to emphasize the fact that the present observations con-

cerning the value of the thymol and colloidal gold tests have been based on the findings in one type of chronic hepatitis. These tests may not prove to have the same value in other types of chronic hepatitis or in other types of liver disease. Furthermore, it has been shown that the responses of cephalin cholesterol flocculation, thymol and colloidal gold tests apparently depend to a large extent on changes in the albumin and/or globulin fractions of the serum proteins (18, 25, 26, 27). A variety of conditions may affect these serum protein fractions and perhaps affect responses of the cephalin cholesterol flocculation, thymol and colloidal gold tests. Thus positive results with these procedures do not necessarily indicate that hepatic involvement is a primary factor in the disease concerned. In fact, it seems possible that positive tests may occur as a result of serum protein changes in certain conditions without hepatic involvement, primary or secondary. The significance of these tests in respect to hepatic disease therefore depends on proper interpretation of the results in relation to the history, physical findings, and the results of other diagnostic procedures. Obviously, positive thymol and colloidal gold tests cannot be regarded as conclusive evidence of chronic hepatitis or other liver disease when the history, physical findings, and results of other diagnostic tests provide no support for or against such a diagnosis. Nevertheless as illustrated by case 2, such findings, in suggesting hepatic disease as a possible etiologic factor, may lead to a correct diagnosis in some illnesses of obscure etiology. Also, if they are found to indicate a specific type of hepatic lesion, their use in conjunction with other tests may eventually enable a more precise definition of the types of hepatic involvement that are present in a given case and this in turn may lead to more accurate diagnoses of specific types of liver disease.

SUMMARY

During the course of investigations of infectious hepatitis induced in human volunteers, 4 cases of chronic hepatitis without jaundice have been observed. In all 4 cases, the chronic form of the disease followed a well-defined attack of acute infectious hepatitis with jaundice, although in case 2, the icterus associated with the acute attack was transient and subclinical. In cases 1, 2, and 3, the acute hepatitis had been induced by the oral administration of a feces preparation known to contain the causative agent of infectious (epidemic) hepatitis and these cases thus were under continuous observation and study both before and after the onset of hepatitis. The 4th case was a hospital patient who had acquired infectious hepatitis under natural circumstances and whose course was similar to that observed in cases 1, 2, and 3 under experimental conditions. In all of these cases, the duration of the illness exceeded 7 months and a diagnosis of chronic hepatitis without jaundice was made on the basis of the history, the clinical manifestations, laboratory evidence of persistent hepatic disturb-

ance, and, in cases 1 and 2, on the microscopic findings in liver biopsy specimens obtained 9 and 6 months respectively after the onset of acute hepatitis. In all of these cases, the course of the disease after the 7th month was one of slow, but progressive, improvement and at the time of writing, cases 1 and 2 appeared to have achieved a complete clinical recovery. The observations on cases 1, 2, and 3 extended over a period of 13, 10, and 9 months respectively. Case 4 was observed only during the 6th and 7th months of her illness. The present report deals with the results of multiple hepatic studies which were conducted at frequent intervals (except for case 4) before and after the onset of hepatitis. In the later stages of the disease in all of these cases, it was found that the commonly used hepatic tests failed to reveal hepatic disturbance although incapacitating symptoms continued and liver biopsies (cases 1 and 2) showed evidence of persistent hepatitis. However, the thymol and colloidal gold tests of MacLagan, which are not yet in common use, remained significantly positive after the results of other hepatic studies (including the cephalin cholesterol flocculation test) had returned to normal. The significance of these findings in respect to the diagnosis of this type of chronic hepatitis is discussed. The data also showed that the thymol flocculation test, which apparently has not previously been used as part of the MacLagan thymol turbidity test in the study of hepatic disease, was a more sensitive indicator of this type of persistent hepatic disturbance than the thymol turbidity test.

A possible explanation for the failure of certain liver function tests to indicate the persistent hepatic disturbance in these cases was suggested by the liver biopsy findings in cases 1 and 2 which showed no evidences of active necrosis or degeneration of the hepatic polygonal cells and no evidence of obstruction of the intrahepatic biliary passages. The principal lesion appeared to be a chronic inflammatory process chiefly involving the portal triads. This process seemed to be the most probable cause of the positive thymol and colloidal gold tests. The observations in these and other cases suggesting that the type of hepatic involvement responsible for positive cephalin cholesterol flocculation tests differs from that responsible for positive thymol and colloidal gold tests are discussed.

CONCLUSIONS

1. Acute infectious hepatitis may be followed by a chronic non-icteric form of the disease that may persist for months and be responsible for continued incapacitating symptoms. In the later stages of this type of the disease, many of the hepatic tests in common use (including the cephalin cholesterol flocculation test) may reveal no evidence of hepatic disturbance. In some such cases, the thymol and colloidal gold tests may be positive, thereby providing valuable diagnostic evidence of persistent hepatic disturbance.

2. Positive thymol and colloidal gold tests due to hepatic disease probably are caused by a different type of hepatic involvement than that responsible for positive cephalin cholesterol flocculation tests.

3. The thymol flocculation test may be one of the most sensitive indicators of certain types of hepatic involvement. It may be significantly positive when the thymol turbidity test is within the normal range and therefore should be included routinely as part of the thymol turbidity test.

4. Positive thymol and colloidal gold tests provide suggestive, but not conclusive, evidence of hepatic disease. Their significance as evidence of hepatic disease depends on proper interpretation in relation to the history, physical findings, and the results of other diagnostic procedures.

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REFERENCES

1. BARKER, M. H., CAPPES, R. B., AND ALLEN, F. W.: J. A. M. A., **129**: 653, 1945. BENJAMIN, J. E., AND HOYT, R. C.: J. A. M. A., **128**: 319, 1945. TURNER, R. H., SNAVELY, J. R., GROSSMAN, E. B., BUCHANAN, R. N., AND FOSTER, S. O.: Ann. Int. Med., **20**: 193, 1944. FISHMAN, A. P.: Bull. U. S. Army Med. Dept., **4**: 457, 1945.
2. NEEFE, J. R., AND STOKES, J. JR.: J. A. M. A., **128**: 1063, 1945.
3. NEEFE, J. R., STOKES, J. JR., BATY, J. B., AND REINHOLD, J. G.: J. A. M. A., **128**: 1076, 1945.
4. (a) NEEFE, J. R., STOKES, J. JR., REINHOLD, J. G., AND LUKENS, F. D. W.: J. Clin. Inves., **23**: 836, 1944. (b) KARR, W. G., REINHOLD, J. G., AND CHORNOCK, F. W.: Manual of Clinical Biochemistry (Stevenson Brothers, Philadelphia) 1942, p. 62. (c) NEEFE, J. R., REINHOLD, J. G., and others: Results of Serial Liver Function Studies in Apparently Normal Persons—to be published.
5. MALLOY, H. T., AND EVELYN, K. O.: J. Biol. Chem., **199**: 481, 1939.
6. DUCCI, H., AND WATSON, C. J.: J. Lab. & Clin. Med., **30**: 293, 1945.
7. GODFRIED, E. G.: Biochem. J., **28**: 2056, 1934.
8. WATSON, C. J., SCHWARTZ, S., SBOROV, V., AND BERTIE, E.: Am. J. Clin. Path., **14**: 605, 1944.
9. WALLACE, G. B., AND DIAMOND, J. S.: Arch. Int. Med., **35**: 698, 1925.

10. QUICK, A. J.: Am. J. Clin. Path., 10: 222, 1940.
11. KINGSLEY, G. R.: J. Lab. and Clin. Med., 127: 840, 1942.
12. BODANSKY, A.: J. Biol. Chem., 101: 93, 1933.
13. REINHOLD, J. G.: Proc. Soc. Exper. Biol. & Med., 32: 614, 1935.
14. HANGER, F. M.: J. Clin. Invest., 18: 261, 1939.
15. NEEFE, J. R., AND REINHOLD, J. G.: Science, 100: 83, (July 28) 1944.
16. MACLAGAN, N. F.: Brit. J. Exp. Path., 25: 15, (Feb.) 1944.
17. KOLMER, J. A., AND BOERNER, F.: Approved Laboratory Technic, D. Appleton Century Company, New York, 4th edition, p. 287.
18. MACLAGAN, N. F.: Nature, 154: 670, (Nov. 25) 1944. Brit. J. Exp. Path., 25: 234, (Dec.) 1944.
19. WATSON, C. J., AND RAPPAPORT, E. M.: J. Lab. & Clin. Med., 30: 983, (Dec.) 1945.
20. WINTROBE, M. M., AND LANDSBERG, J. W.: Am. J. Med. Sc., 189: 102, 1935.
21. SHANK, R. E., AND HOAGLAND, C. L.: J. Biol. Chem., 162: 133, (Jan.) 1946.
22. COHN, C., AND LIDMAN, B. I.: J. Clin. Invest., 25: 145, (Jan.) 1945.
23. NEEFE, J. R., AND REINHOLD, J. G.: Unpublished data.
24. NEEFE, J. R.: cited by Bockus, H. L.: Gastroenterology, W. B. Saunders Co., Vol. III, 1946, p. 1062.
25. MOORE, D. B., PIERSON, P. S., HANGER, F. M., AND MOORE, D. H.: J. Clin. Invest., 24: 292, (May) 1945.
26. GRAY, S. J.: Proc. Soc. Exper. Biol. and Med., 51: 400, 1942.
27. KABAT, E. A., HANGER, F. M., MOORE, D. H., AND LANGDON, H.: J. Clin. Invest., 22: 563, 1943.

A STUDY OF THE TIME OF "HEALING" OF PEPTIC ULCER IN A SERIES OF SIXTY-NINE CASES OF DUODENAL AND GASTRIC CRATERS¹

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INTRODUCTION

A reasonably accurate determination of the time of healing of a peptic ulcer has both practical and theoretical value. The establishment of such a healing time would serve as a base-line for evaluation of the efficacy of therapy in an individual case as well as offer an objective standard for comparison of new treatments. From a physiological point of view, it has been conjectured that the power of peptic ulcers experimentally produced by excision in the dog and cat, and the non-ulcer bearing human patient to heal is of the same order of magnitude as that of ulcers occurring as a disease process in man but that the ulcer patient requires special conditions such as rest, diet, acid neutralization, etc., in order to obtain optimum healing. This question could be settled if the healing time of human peptic ulcer were known, since the rate of healing of experimental ulcers produced by excision in dogs and cats has been reported frequently, and a few cases have been reported in man. The purpose of this paper is to present sufficient, controlled data which have not as yet appeared in the literature for the estimation of the rate of healing of human peptic ulcer and from which conclusions can be drawn.

REVIEW OF THE LITERATURE

There is a paucity of information in the literature regarding the healing time of peptic lesions. Observations on the healing process are either limited to a few cases, or the studies were not done primarily with this problem in mind, or the therapeutic control of the reported cases was poor or combinations of these objections exist.

Healing times were noted by several authors in evaluating special methods of treatment. Among these are Buckstein (1) who described a case of gastric crater treated by frequent duodenal tube feedings which was subsequently visualized at the end of 6 weeks of treatment and questionably seen also at 8 and 15 weeks. Einhorn (2) also reported disappearance of the niche in 5 cases of gastric ulcer in 2, 2, 4, 7 and 10 weeks after management by duodenal feed-

¹ These cases were compiled from the records of Percy Jones General Hospital, Battle Creek, Michigan, while one of us (G. M. C.) was stationed there. The authors wish to thank Capt. L. H. Bernstein, M.C., assistant chief of the x-ray department, for his valuable aid, Col. C. B. Whims M.C., chief of the medical service, and Major G. R. Joyner, M.C., assistant chief of the medical service, for their cooperation and assistance.

ings. Fifteen cases of gastric ulcer were followed gastroscopically by Freeman (3) in evaluating duodenal feeding therapy; he reported the average time of disappearance of the crater gastroscopically as 4 weeks, but added that some cases required a "little longer time"; a control case on a "gastric diet" instead of duodenal feedings still showed the lesion present after 6 weeks. Tui et al. (4) in evaluating their use of protein hydrolysate and Dextri-Maltose feeding treatment reported the radiological disappearance of 4 duodenal craters in from 10 to 25 days after treatment and the average disappearance time of 8 gastric lesions as 19 days with a range of 10 days to 1 month; 3 other gastric craters were smaller in 10 to 15 days.

Several writers reported data on healing time but their repeat x-ray studies were done at intervals too long for accurate estimation. Hamburger (5) reported a case each of gastric and duodenal ulcer which were checked by x-ray after 3 months' treatment and found to have disappeared. Diamond (6) also presented evidence of crater disappearance after treatment with a modified Lenhartz diet in 10 gastric ulcers in from 2 months to 2 years; another of his cases revealed x-ray disappearance of the crater in 3 weeks and another in 7 weeks. Nicholas and Moncrieff (7) using an average time of 6 months between their first and second x-ray examinations presented 11 cases of "healed" gastric craters after 6 months of undescribed treatment; 4 more craters had decreased in size but were found healed $3\frac{1}{2}$ months later and 2 had remained stationary, one of which was subsequently found to be healed after another $3\frac{1}{2}$ months' treatment; 4 recurrences of the 11 "healed" craters were noted $9\frac{1}{2}$ months after their original films; no correlation could be found between duration of symptoms and time of healing. White (8) concluded that age had no effect on healing (age range was 40 to 60 years) and that the size of the crater and duration of symptoms also had no effect; he reported disappearance of 3 medium-sized gastric craters in from 2 to 6 months, 2 large gastric craters in 1 to 6 months and 1 small stomach ulcer in 1 week; he used a modified Sippy diet.

Healing time was mentioned incidentally by several authors. Brown (9) mentioned the disappearance of 2 craters in the stomach in 12 weeks and in 37 days after a strict Sippy regime. The disappearance of 1 gastric and 2 duodenal craters was noted by Golden (10) in 44 days, 3 weeks and 6 months, respectively, after bed rest and Sippy diet. No radiological evidence of crater was found by Hurst and Briggs (11) in 3 gastric cases after treatment of undisclosed nature for 1 month, 2 months and 3 years. Tanner (12) made the general statement that gastric ulcers will heal gastroscopically in 3 to 6 weeks in some cases of acute, subacute and moderate-sized chronic lesions but added that many lesions heal slower; he reported a case of gastric crater that became less than one-fourth its original size in 3 weeks and another that remained unhealed in 12 weeks; no details as to type of treatment was included. Employing a modified

Sippy therapy, Dale and Redichen (13) found that 4 to 9 weeks of treatment were required for disappearance of the niche in 5 gastric cases and 6 weeks in 2 duodenal cases.

The largest numbers of cases were reported by Ohnell (14) and by Templeton (15). The former recorded disappearance of the niche in 33 cases of gastric ulcers in an average of 40 days (range 14 to 100 days) after rigorous treatment consisting of 6 weeks of bed rest and a diet of milk, cream, eggs and fish with Vichy water; he stated that large craters tended to heal slowly but there was poor correlation between size of crater and rate of healing; no attempt was made in this study to take repeat films at specific time intervals. Templeton reported the disappearance of the crater in 36 duodenal ulcers in from 1 to 20 days; again, he could make no correlation between size of crater and time of healing; there is no mention made by this author of the frequency of x-ray examinations nor the amount or type of treatment given.

DESCRIPTION OF CASES

The 69 cases in this series were diagnosed and treated at an Army General Hospital from October 1944 to February 1946. Most of the patients were evacuees from overseas hospitals, 19 with the transfer diagnosis of peptic ulcer and the remainder with various other medical and surgical conditions diagnosed. Six of the patients originated from the command, 3 were German Prisoners-of-War working at the hospital and one was a civilian dependent. All were males with the exception of one member of the W.A.C. The average age was 31 years with extremes of 22 to 66 years. There were 63 duodenal craters and 6 gastric craters.

Treatment was begun shortly after the diagnosis was established by x-ray examination. Over three-fourths of the x-ray studies were done by the same roentgenologist; fluoroscopic study and serial roentgenograms were taken on all original and subsequent examinations. This period between the original radiological study and the institution of treatment did not exceed 3 days and in the majority of cases was between 1 and 2 days. It is to be emphasized that all of the patients were placed upon the same therapeutic regime, with a few exceptions noted below, which consisted of the following features: (1) bed rest for 3 days followed by activities confined to the ward; one dram of a mixture of sodium bicarbonate and calcium carbonate in proportion 1:3 in water every 2 hours from 8:00 A.M. to 8:00 P.M., at 1:00 A.M. during the first week of treatment and at night if awakened; the administration of alkalies continued on this schedule for 28 days, following which, they were given 30 minutes after meals, before retiring and on awakening at night; (2) half-and-half mixture of milk and cream, 6 ounces, every 2 hours from 7:00 A.M. to 9:00 P.M. for the first 28 days of the regime, following which the mixture was given between meals

and in the evening; (3) food by mouth was begun on the fourth day by the gradual addition of farina, poached or boiled eggs, toast, pureed vegetables and ground, boiled or broiled beef. This continued over a period of 28 days and by the 16th day, the patients were eating 6 small meals a day and 3 meals per day by the 22nd day of the regime; after the 28th day the patients ate 3 normalized meals a day in the special diet mess hall, which excluded highly seasoned and fried foods; (4) for the first 28 days tincture of belladonna, 15 drops thrice daily, one half grain of phenobarbital thrice daily, and one multivitamin capsule daily were given; (5) the smokers were encouraged to decrease or eliminate their use of tobacco. Departures from the above schedule were few, were made for clinical reasons and included institution of 2 hourly alkaline medications during the night for night pain in 2 cases; substitution of calcium carbonate for the mixed alkali because of impending alkalosis in 1 case; withholding of food for 5 instead of 3 days in one case of massive hemorrhage, continuation of the rigorous treatment for periods up to 10 weeks in 6 cases because of positive x-rays or exacerbation of symptoms. The treatment was directly supervised by one of us (G. M. C.) in all but one case. With the exception of 6 cases, all became asymptomatic and remained so after 2 to 7 days' treatment.

Repeat x-ray examinations were scheduled routinely following completion of the 28 day regime; these studies were done in 1 to 5 days after being requested. In 12 cases repeat films were made prior to completion of the prescribed rigorous treatment of 28 days and these cases will be discussed later in the paper. All of the army patients were separated from the service and follow-up examinations were not done.

RESULTS

Definition of "Healing Time": In this study the expression "healing time" is used to designate the time interval between our original visualization of the crater by roentgen studies and its subsequent non-visualization following strict medical treatment.

Limitations: There are difficulties in attempting to ascertain the time of healing of human peptic ulcers. Indeed, most roentgenologists hesitate to say when a duodenal ulcer is healed radiologically because of the lack of definite objective signs of healing. However, by using the time of disappearance of a previously seen crater an objective yard-stick is obtained. The question as to whether secondary radiological signs of duodenal ulcer such as deformity, tenderness and irritability indicate non-healing has not been a factor in determining "healing time" in this paper.

Regarding gastric lesions, there are 2 cases of gastric ulcer reported in the literature which were examined histologically soon after disappearance of the

TABLE 1

Duodenal

CASE NO.	AGE	MILITARY SERVICE	DURATION OF SYMPTOMS	DATE CRATER VISUALIZED	SIZE OF CRATER	LOCATION OF CRATER	DATE CRATER NOT VISUALIZED	"HEALING" TIME	DATE PREVIOUS POSITIVE X-RAY DIAGNOSIS
1	33	7 9/12	24	12/18/44	S	mid portion	1/22/45	35	
3	35	5		11/14/44	S	lesser curvature	1/13/45	60	
4	25	3 8/12	6	6/ 3/45†	S		7/ 4/45	31	
5	27	8/12	8	10/ 9/44	L	mid portion	10/30/45	21	
6	25	3	84	1/ 4/45	S	lesser curvature	2/15/45	42	April 1944
7	39	3 5/12	18	3/13/45	S		4/13/45	31	
8	24	2 9/12	10	8/14/45	S	lesser curvature	9/10/45	27	April 1945‡
9	26	2 8/12	20	1/27/45	S	base	3/19/45	51	
10	39	2 1/12	6	4/ 9/45	S	apex	5/10/45	31	Feb. 1945‡
11	37	2 1/12	2	5/ 4/45	S	posterior wall	6/14/45	41	
12	30	4 7/12	48	7/ 4/45	S	mid portion	8/17/45	44	
13	26	1 5/12	27	6/29/45	S	apex	8/27/45	59	
14	25	3 6/12	12	10/11/45	S	base	11/15/45	35	May 1945
15	22	2/12	2	8/23/45	S	mid portion	9/21/45	29	June 1945§
16	39	3	36	4/19/45	S	posterior wall	6/26/45	68	April 1942
18	38	3	9	9/21/45	L	mid portion	10/18/45	27	May 1945‡
20	30	4	4	6/ 6/45	L	mid portion	7/25/45	49	Jan. 1945‡
21	28	2	72	5/23/45	S	mid portion	7/ 3/45	41	
22	36	2 8/12	96	7/26/45	S	posterior wall	9/ 6/45	42	Feb. 1945
23	30	2 5/12	5	6/21/45	S	mid portion	7/25/45	34	1944
25	27	2		6/28/45	S	mid portion	8/30/45	63	
26	27	2 3/12	44	4/ 7/45	S	mid portion	6/ 4/45	58	Oct. 1941
27	31	2 5/12	1	8/31/45	S	mid portion	10/10/45	40	
28	37	1 1/12	6	4/20/45	S	mid portion	5/21/45	31	Sept. 1944
29	25	1 11/12	10	5/ 7/45	S	mid portion	6/19/45	43	
30	32	2	15	7/30/45	S	base	9/26/45	58	
31	25	3 8/12	6	7/19/45	S	lesser curvature	8/27/45	39	
32	26	1 8/12	5	5/17/45	M	lesser curvature	6/14/45	28	
33	36	4	1	6/ 5/45	S	posterior wall	7/17/45	42	
34	28	2 2/12	24	9/12/45	S	mid portion	10/19/45	37	Feb. 1943‡
35	29	3 6/12	2	12/28/45	M	mid portion	2/ 4/46	38	
37	30	2 8/12	11	8/31/45	S	lesser curvature	10/18/45	48	
38	28			1/28/45	S	mid portion	2/26/45	28	
39	66	*	12	3/29/45	L	mid portion	11/14/45	230	
40	22	1 11/12	1	2/ 3/45	S	base	2/27/45	24	
41	30	2 6/12	5	9/28/45	S	lesser curvature	10/30/45	32	
42	30	3 11/12	18	9/25/45	M	mid portion	10/26/45	31	
43	31	2 8/12	84	9/17/45	S	mid portion	11/ 7/45	51	April 1945‡
44	29	1	48	10/27/45	M	mid portion	12/ 7/45	41	
45	36	1	60	3/26/45	S	apex	5/ 1/45	36	
46	30	3 1/12		10/25/45	S	mid portion	12/ 7/45	43	
47	24	2 11/12	30	11/12/45	S	mid portion	12/19/45	37	
48	33	2 7/12	6	11/26/45	S	apex	12/28/45	32	
49	30	6/12	42	11/16/45	S	mid portion	12/20/45	34	
50	38	2 8/12	144	4/ 5/45	L	mid portion	5/16/45	41	

Table 1—Concluded

CASE NO.	AGE	MILITARY SERVICE	DURA-TION OF SYMP-TOMS	DATE CRATER VISUALIZED	SIZE OF CRATER	LOCATION OF CRATER	DATE CRATER NOT VISUALIZED	"HEALING" TIME	DATE PREVIOUS POSITIVE X-RAY DIAGNOSIS
51	25	2 2/12	72	3/17/45	S	apex	4/27/45	41	
52	23	3 4/12	12	3/22/45	S	mid portion	4/ 4/45	13	
53	40	2 7/12	14	3/16/45	L	mid portion	4/19/45	34	
54	24	2 8/12	78	4/ 9/45	S	apex	5/14/45	35	Jan. 1945†
55	26	4 2/12	6	6/ 5/45	S	base	7/11/45	36	Dec. 1944‡
56	39	3	6	3/21/45	S	mid portion	5/ 8/45	48	
57	29	4 8/12	18	9/19/45	L	mid portion	10/24/45	35	
58	38	2 2/12	18	3/13/45	S	base	4/20/45	38	
59	39	2 9/12	9	12/14/45	S	posterior wall	1/16/46	33	Mar. 1944‡
60	39	3 5/12	18	12/12/45	S	base	1/15/46	34	
61	24	3 1/12	11	12/19/45	M	apex	1/24/46	36	Nov. 1945
62	33	2 9/12	12	1/14/46	M	greater curvature	2/ 6/46	23	
63	27	3	2	12/17/45	S	mid portion	1/ 7/46	21	
64	24	3 6/12	1	12/ 3/45	S	posterior wall	1/ 8/46	36	Nov. 1945‡
65	32	3 1/12	5	9/25/45	M	mid portion	10/18/45	23	
67	59	4 2/12	15	8/ 6/45	S	base	9/ 1/45	26	
68	27	4 4/12	13	10/ 1/45	L	mid portion	11/ 6/45	36	
69	25	3 3/12	6	9/11/45	S	mid portion	10/23/45	42	

* Civilian dependent.

† Perforation closed surgically.

‡ Crater.

§ Perforation of stomach closed surgically—no initial x-ray studies done.

|| S = 3-5 mm.

M = 6-8 mm.

L = 9-21 mm.

crater and showed almost but not complete re-epithelialization (16). Gastroscopic correlation of healing has been described in 18 cases (15, 17); 12 of these revealed re-epithelialization soon after disappearance of the niche and 5 showed shallow craters still present. No such correlative data are available for duodenal ulcers.

According to the scheme employed in obtaining repeat films after 4 weeks of active treatment, the "healing time" so computed is not the minimum one. It would have been necessary to obtain frequent film studies every 3 to 4 days during treatment to obtain this minimum "healing time" and such a procedure was not practical under the prevailing conditions. Crater disappearance was noted in 12 patients, however, in from 1 to 16 days prior to completion of treatment. In 5 cases repeat x-rays at the prescribed time following the 4 weeks of treatment showed the crater still present in from 8 to 92 days. Statistically, the average of the "healing times" of these two special groups of 17 cases was about the same as the average for the whole group. It is believed that the

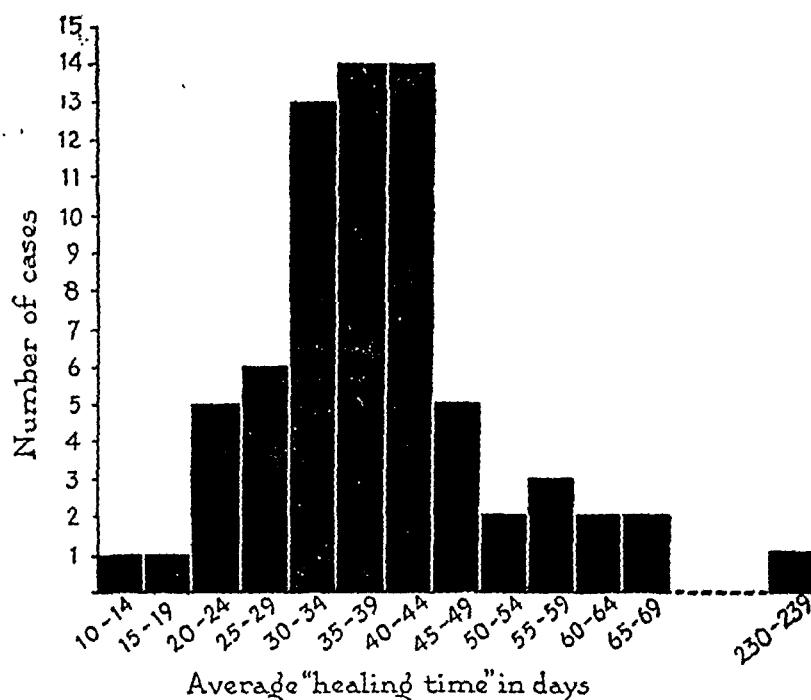


FIG. 1. AVERAGE "HEALING TIME" OF DUODENAL AND GASTRIC ULCERS (69 CASES)

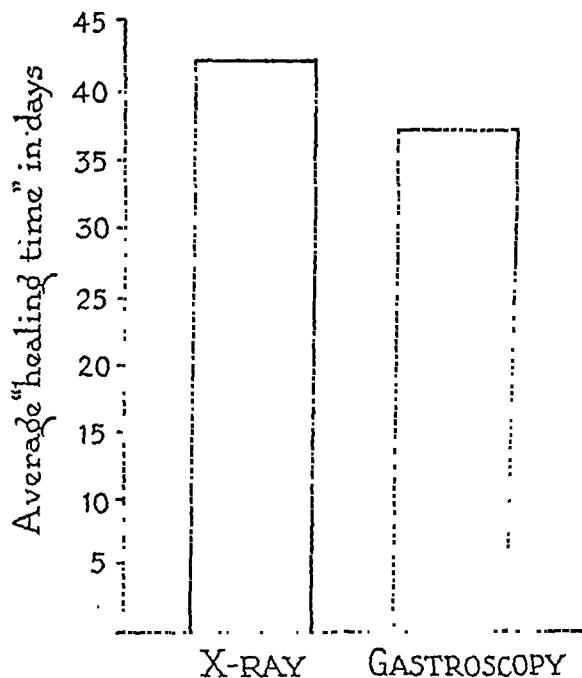


FIG. 2. AVERAGE "HEALING TIME" OF GASTRIC CRATERS DETERMINED BY X-RAY (6 CASES) AND GASTROSCOPY (3 CASES)

times of crater disappearance as obtained in this study closely approximate the minimum "healing time."

Seventeen patients in this series were evacuated to this General Hospital with the transfer diagnosis of peptic ulcer. However, a careful review of their past histories showed that, with the possible exception of one questionable case, all had had either no active or no effective treatment before our diagnosis, so that our computed "healing times" would not be inaccurately lengthened because of previous healing. Obviously, it is impossible to determine how long a crater was present prior to the initial demonstration of it, so variations due to this factor cannot be estimated.

TABLE 2

Gastric

CASE NO.	AGE	MILITARY SERVICE	DURATION OF SYMPTOMS	DATE CRATER VISUALIZED	SIZE OF CRATER	LOCATION OF CRATER	DATE CRATER NOT VISUALIZED	"HEALING" TIME	DATE PREVIOUS POSITIVE X-RAY DIAGNOSIS
2	22	2/12	4 hours	6/16/45§	S	lesser curvature antrum	8/23/45	days 68	
17	35	4 6/12	8 months	9/13/45	L	lesser curvature middle third	10/16/45*	32	
19	28	1 10/12	120 months	10/11/45	S	lesser curvature antrum	10/29/45	18	
24	31	5/12	8 hours	4/ 8/45§	S	lesser curvature antrum	5/24/45	46	
36	24	4	6 months	12/20/45	S	greater curvature antrum	2/ 4/46†	46	
66	42	15		9/12/45	L	greater curvature antrum	10/26/45‡	44	

* Gastroscopy 10/17/45 showed small unhealed crater; healed 10/21/45.

† Gastroscopy 12/24/45 revealed the crater; granulation plug on 1/11/46; lesion healed 2/12/46.

‡ Gastroscopy 9/15/45 showed crater; healed 10/3/45.

§ Perforation of stomach closed surgically—no initial x-ray studies done.

"Healing Time": The average "healing time" for the 63 duodenal craters was 40 days with a range of 13 to 230 days. One case, No. 39 (see table 1), required 230 days for x-ray disappearance of the crater—this was far out of the distribution range of the remainder of the cases (fig. 1). The average "healing time" excluding this case was 37 days with a range of 13 to 68 days. The average time for the disappearance of the 6 gastric craters by x-ray was 42 days with range of 18 to 68 days. Three of these cases were followed gastroscopically and the average "healing time" determined by this means was 37 days with range of 21 to 52 days (fig. 2).

Case No. 19 (see table 2) was gastroscoped frequently during treatment and it was found that the lesion was still present, though small, the day following

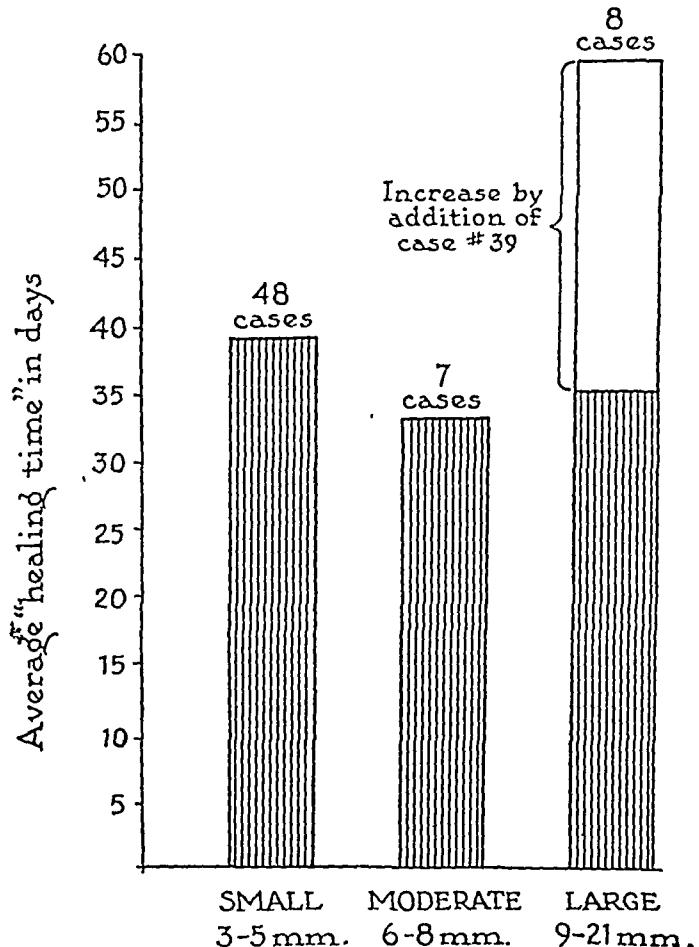


FIG. 3. AVERAGE "HEALING TIME" OF SMALL, MODERATE AND LARGE DUODENAL CRATERS (63 CASES)

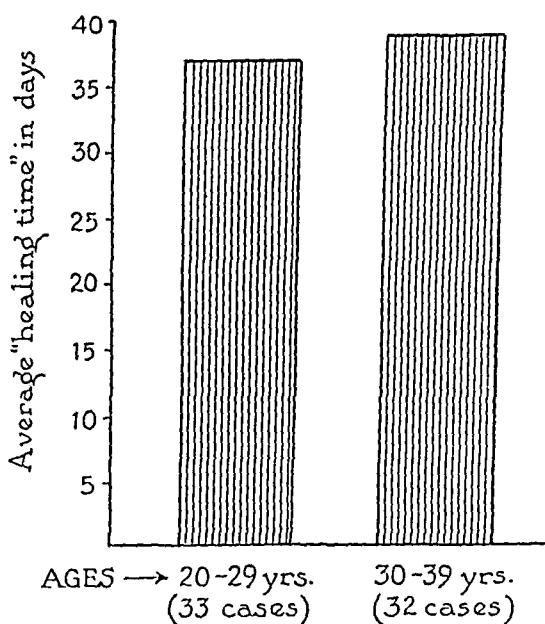


FIG. 4. AVERAGE "HEALING TIME" OF AGE GROUPS 20-29 AND 30-39 YEARS

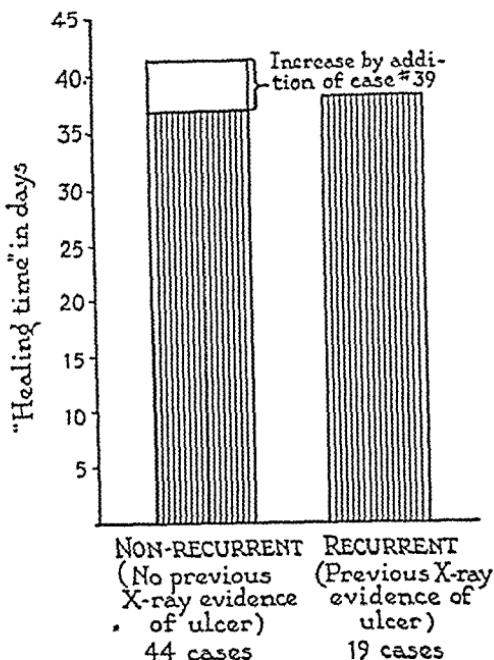


FIG. 5. AVERAGE "HEALING TIME" OF RECURRENT AND NON-RECURRENT DUODENAL ULCERS

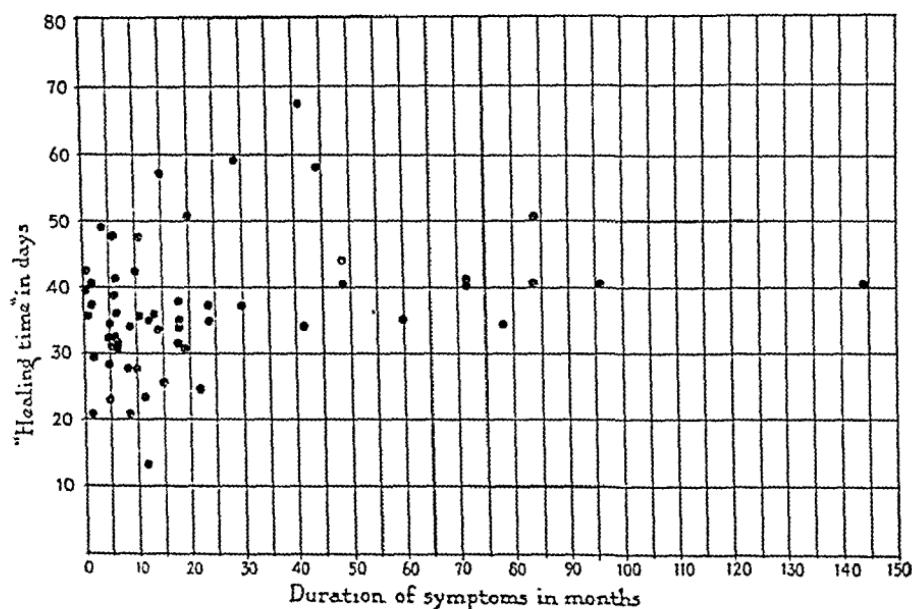


FIG. 6. SCATTERGRAM OF "HEALING TIME" AND DURATION OF SYMPTOMS IN 58 DUODENAL CRATERS

negative x-rays; 6 days later, however, re-epithelialization had become complete. Another, Case No. 66 (see table 2), was gastroscoped twice, the first examination revealed the crater and the second, 18 days later, showed complete healing; repeat x-ray studies in this case were not done, however, until 23 days after the negative gastroscopy. The third case, No. 36, was gastroscoped 3 times and the crater was first seen 4 days after the positive x-ray; 18 days later a small "plug" of what appeared to be granulation tissue was seen protruding from the edges of the crater which had disappeared with complete healing 1 month later. Repeat x-ray taken 46 days after the original film revealed no crater.

The distribution of "healing times" is shown in figure 1. Over 50 per cent of the cases fall into the range of 30 to 44 days' "healing time."

Size of Crater: The craters were divided into 3 groups as to size—small, moderate and large. The small-sized lesions measured about 3 to 5 mm. in diameter (not depth), the moderate about 6 to 8 mm., and large up to 21 mm. No correlation was found between size of crater and rate of healing (fig. 3). Thirty-two of the duodenal craters were located in the mid portion of the bulb.

Age: This study deals with a selected age group—that of military service in war time. Ninety-four per cent of the patients were in the third and fourth decade. Figure 4 shows no correlation between age and "healing time" in this age range.

Recurrence: Nineteen cases were known to have had previous x-ray diagnoses of peptic ulcer, in 10 of whom craters had been visualized. No correlation can be made between recurrence of peptic ulcer and "healing time" as seen in figure 5.

Duration of Symptoms: Figure 6 illustrates the lack of correlation between "healing time" and duration of ulcer symptoms.

DISCUSSION

The results set forth above provide factual support to the commonly expressed impression that chronic duodenal or gastric ulcers in man usually heal rapidly under conditions of strict medical management. This observation is of great significance in the light of experimental observations on animals, and its implications have hitherto been unrecognized.

When the healing time of an experimental excision ulcer of the pyloric or duodenal mucosa of the dog (18) is compared with the usual rate of filling of a crater of a duodenal or gastric ulcer in man under strict medical management, the difference is not striking. Similarly the healing time of an excision ulcer of the stomach of the rabbit on rough food (19) is comparable to the filling time of the crater of a gastric ulcer in man.



FIG. 7. CASE NO. 17. ROENTGENGRAM TAKEN SEPTEMBER 13, 1945 SHOWING CRATER OF LESSER CURVATURE

There are actually only two differences between the healing of an excision ulcer in the dog and a "chronic" peptic ulcer in man. *One* is that in most ulcer patients, "favorable conditions" are required for prompt healing; the *second* is

that in some ulcer patients the lesion heals very slowly, and occasionally perforates or erodes a blood vessel even under "favorable conditions." These two



FIG. 8. CASE NO. 17 REPORT FILM TAKEN OCTOBER 16, 1945, FOLLOWING TREATMENT SHOWING DISAPPEARANCE OF PREVIOUSLY VISUALIZED CRATER (SEE FIGURE 7)

factors are related to the striking tendency of peptic ulcer in man to recur after it has healed.



FIG. 9. CASE NO. 27. FILM TAKEN AUGUST 31, 1945 PRIOR TO TREATMENT REVEALING A SMALL POST-PYLORIC CRATER

Approximately 20 per cent retention of the barium was noted in the stomach after six hours.

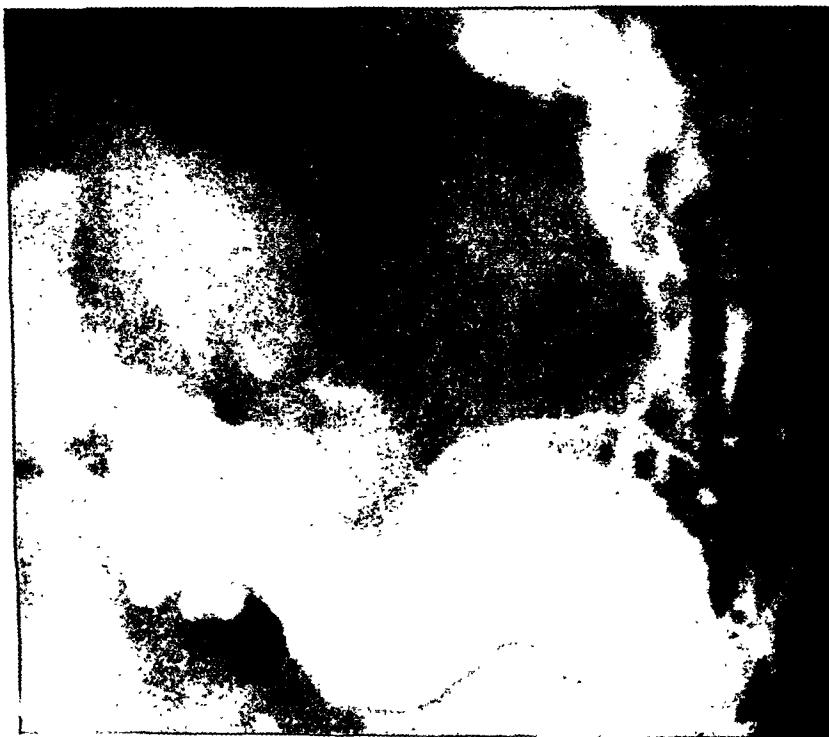


FIG. 10. CASE NO. 27. REPEAT FILM TAKEN OCTOBER 10, 1945 AFTER TREATMENT. CRATER IS NOT VISUALIZED, BUT A TYPICAL PINE-CONE DEFORMITY EXISTS. (SEE FIGURE 9)

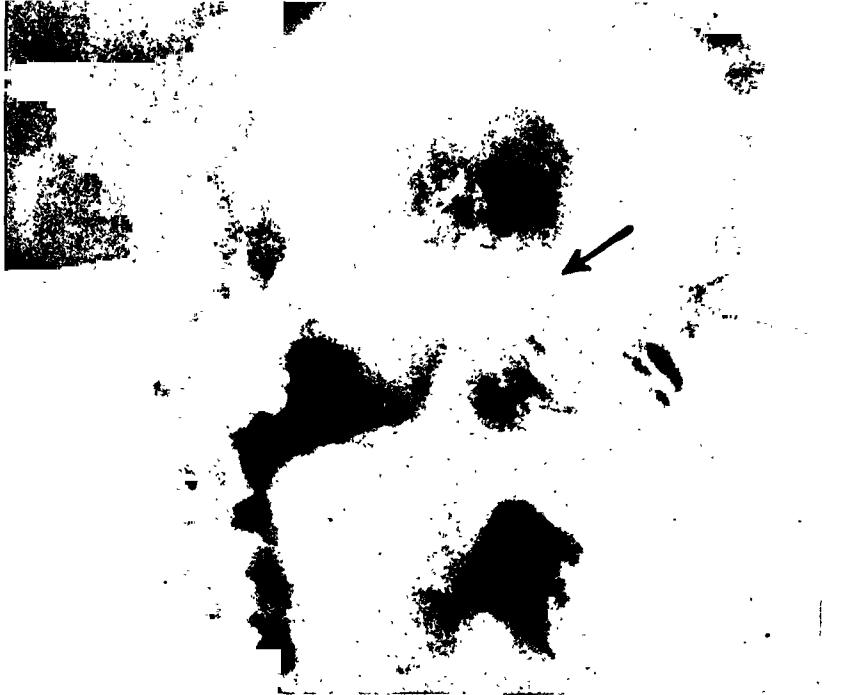


FIG. 11. CASE NO. 18. ROENTGENOGRAM TAKEN SEIT. MBIR 21, 1945 SHOWING A LARGE CRATER IN THE MID-PORTION OF A POORLY-FILLED BULB



FIG. 12. CASE NO. 18. REPEAT FILM TAKEN OCTOBER 18, 1945 SHOWING NO CRATER AND A NORMAL APPEARING BULB (SEE FIGURE 11)



FIG. 13. CASE NO. 20. FIRST FILM TAKEN JUNE 6, 1945, BEFORE TREATMENT REVEALING A LARGE CRATER IN THE MIDDLE ONE-THIRD OF THE BULB



FIG. 14. CASE NO. 20. SECOND FILM TAKEN JULY 3, 1945 AFTER COMPLETION OF FOUR WEEKS TREATMENT SHOWING A SMALL CRATER WITH BEGINNING PSEUDO-DIVERTICULUM FORMATION (SEE FIGURE 13)

CONCLUSIONS

1. The determination of "healing time" of peptic ulcer is important, practically, for evaluation of new methods of treatment and for judging the efficacy of treatment in an individual case and, theoretically, for comparison of the healing power of peptic ulcers in man and lower animals.
2. A review of the literature reveals that accurate data on the rate of healing are not available.

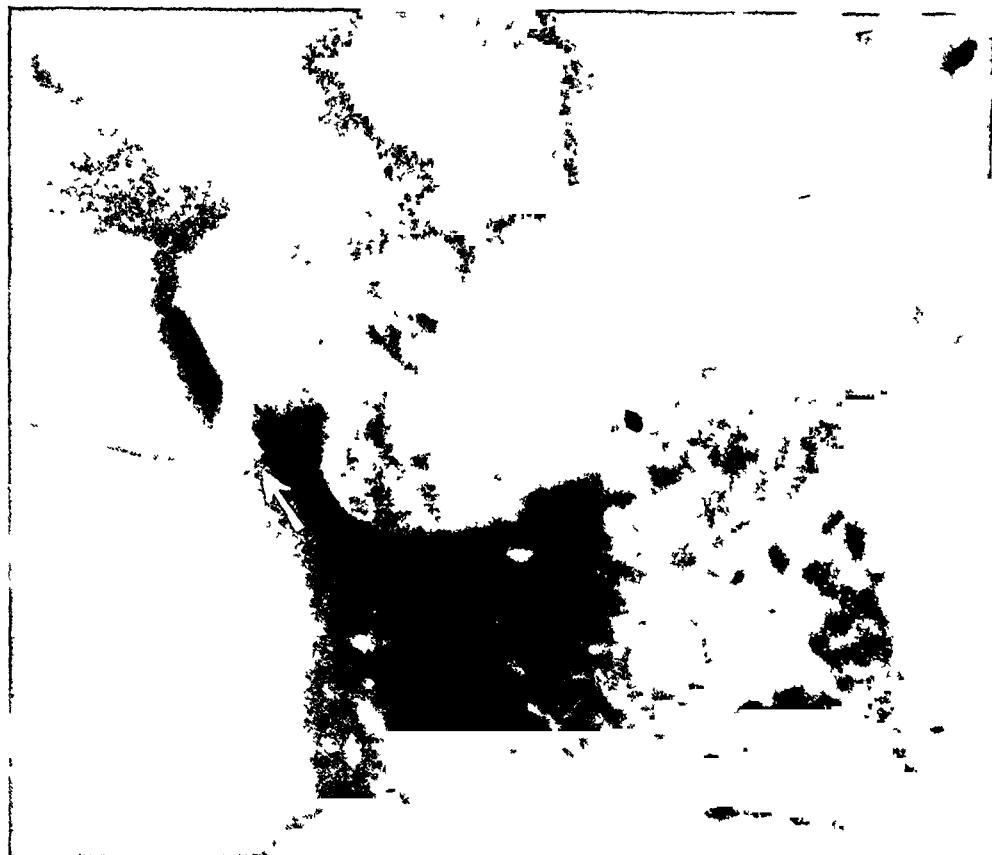


FIG 15 CASE NO 20 THIRD FILM TAKEN JULY 25, 1945 SHOWING NO CRATER BUT REVEALING A WELL DEVELOPED PSEUDO DIVERTICULUM (SEE FIGURES 13 AND 14)

3. The "healing time" as judged by the time of disappearance of the crater radiologically as done in this series has its limitations of interpretation
4. The data on the estimation of the "healing time" for a series of 63 duodenal and 6 gastric craters are presented. The average "healing time" for the former group was 37 days and the latter 42 days by x-ray. Treatment, time of x-ray examinations and roentgen studies were standardized as much as possible.
5. A comparison of the estimation of "healing time" by x-ray and gastroscopy in gastric craters is discussed
6. No correlation was found between the "healing time" and the size of the crater, age, recurrence or duration of symptoms.

REFERENCES

1. BUCKSTEIN, J.: X-ray evidence of ulcer healing. *J. A. M. A.* **76**: 231, 1921.
2. EINHORN, M.: Über peptische Geschwüre mit Deformität des Organs (durch x-strohlen festgestellt) welche durch Behandlung zum Bessern Berändert worden sind. *Arch. f. Verdauungskr.* **30**: 175, 1922.
3. FREEMAN, H.: Gastroscopic control of treatment of gastric ulcer by duodenal feeding. *Brit. J. Surg.*, **32**: 303, 1944.
4. TUI, CO., WRIGHT, A. M., MULHOLLAND, J. H., GALVIN, T., BARCHAM, I. AND GERST, G. R.: The hyperalimentation treatment of peptic ulcer with amino acids (protein hydrolysate) and Dextri-Maltose. *Gastroenterology* **5**: 5, 1945.
5. HAMBURGER, W. W.: Roentgenological studies in the healing of gastric and duodenal ulcers. *Am. J. M. Sc.* **155**: 204, 1918.
6. DIAMOND, J. S.: Observations on the curability of gastric ulcer with a report of 14 cases of healed lesser curvature ulcers. *Am. J. M. Sc.* **163**: 548, 1922.
7. NICHOLAS, F. G., AND MONCRIFF, A.: The healing of gastric ulcers: radiological observations. *Brit. M. J.* **1**: 999, 1927.
8. WHITE, F. H.: Observations on the healing of gastric ulcer. *New England J. M.* **201**: 1075, 1929.
9. BROWN, R. C.: Ulcer of the stomach and duodenum. *The Oxford Medicine III: Part 1*, 123, 1936, The Oxford U. Press, N. Y., N. Y.
10. GOLDEN, R.: The roentgen ray examination of the digestive tract I: 265, 1941, in *Diagnostic Roentgenology*, Ross Golden editor, Thomas Nelson and Sons, N. Y., N. Y.
11. HURST, A. F., AND BRIGGS, P. V.: The diagnosis of gastric and duodenal ulcer with the x-rays. *Guy's Hosp. Reports* **74**: 278, 1924.
12. TANNER, N. C.: A critique of gastroscopy, *Brit. M. J.* **2**: 849, 1944.
13. DALE, T., AND REDICHEN H. G.: En klinisk-rontgenologisk studie over resultative av den interne behandling av ulcers ventriculi at duodeni. *Norsk, Mag. f. Saegevid* **95**: 585, 1934.
14. OHNELL, H.: Interne Behandlung bei ulcerus ventriculi mit röntgenologischer Nizche. *Acta Med. Scand.* **52**: 1, 1920.
15. TEMPLETON, F. E.: X-ray examination of the stomach, 1944, U. of Chicago Press, Chicago, Ill.
16. CROHN, B. B., WEISKOPF, S., AND OSCHNER, P. W.: The healing of gastric ulcers. *Arch. Int. Med.* **37**: 217, 1926.
17. TEMPLETON, F. E., AND SCHINDLER, R.: Roentgenologic and gastroscopic studies in chronic gastritis and peptic ulcer. *Am. J. Roentgenol.* **41**: 354, 1939.
18. IVY, A. C.: Studies on gastric and duodenal ulcer. *J. A. M. A.* **75**: 1540, 1920.
19. FERGUSON, A. N.: A cytological study of the regeneration of gastric glands following the experimental removal of large areas of mucosa. *Am. J. Anat.* **42**: 403, 1928.

NOCTURNAL GASTRIC SECRETION

II. STUDIES ON NORMAL SUBJECTS AND PATIENTS WITH DUODENAL ULCER¹

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INTRODUCTION

Part I of this study (1) summarized the results of our investigations of nocturnal gastric secretion in 38 normal subjects (73 studies) and 29 patients with duodenal ulcer (77 studies),—a total of 150 nocturnal gastric secretion studies. It included our views on the practical implications of nocturnal secretion as they relate to the medical and surgical management of duodenal ulcer.

The present publication (Part II) includes the tables, charts, graphs and sections which were omitted from the Journal of the American Medical Association publication (Part I). In addition, we comment on the physiological phases of our studies.

PART II

Historical

Only a limited amount of work has been done on nocturnal gastric secretion in human beings. Beaumont (2) was unable to find gastric juice in the unstimulated stomach of Alexis St. Martin. Chalfen (3) reported that both the amount and the acidity of gastric secretion were reduced during sleep but increased on arising in the morning. He noted higher acid value in patients with peptic ulcer. Winkelstein (4) reported that normal subjects secrete only a small amount of gastric juice during the night with a low concentration of acid but added that ulcer patients have a higher nocturnal curve and high titer of acid. Cornell, Winkelstein and Hollander (5) subsequently repeated these studies and concluded that patients with uncomplicated duodenal ulcer secrete a large amount of highly acid juice during the night. Normal subjects, they concluded, "showed little or no free hydrochloric acid and specimens were difficult to obtain in most instances because of the small amount of night secretion." Val Dez (6) noted that during the night ulcer patients have a larger amount of secretion and a higher concentration of acid than normal persons. Mears (7) agrees with this view. Henning and Norpeth (8), however, claim that a variety of gastric acidity curves may be obtained both in normal subjects and in patients with duodenal ulcer and that, while most of their ulcer patients showed an increase in quantity of gastric juice of high acid value, several showed

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no secretion after midnight. Hellebrandt and her associates (9) reported that a normal fasting human stomach secretes continuously day and night and that the acidity of the fasting secretion rises and falls intermittently in the absence of all intentional stimulation.

Different opinions, therefore, have been expressed concerning the quantity of gastric juice secreted by normal persons during the night. However, the consensus is that ulcer patients during the night secrete a greater volume of gastric juice and that the juice is of a higher acid concentration than in normal persons.

Methods

Subjects studied. The normal subjects were young men and women, mainly college students and internes, in good health at the time of study. All ulcer patients were men with mild ulcer distress who presented symptoms of uncomplicated duodenal ulcer when the studies were being conducted. Studies were not carried out on either normal or ulcer subjects who showed signs of having a cold or any infection. The subjects remained in bed at Harper Hospital throughout the night, and slept in the interim between aspirations. The subjects who were subjected to continuous gastric aspiration were not disturbed throughout the night. Smoking and the drinking of fluids other than those given at meal-time were prohibited during the periods of study.

Meals. The two types of meals used consisted of foodstuffs which are fairly representative of the average American dietary but contained a minimum amount of cellulose. The meals were specially designed to eliminate mechanical difficulties in withdrawing gastric contents through the gastric tube (Levine type). Particular attention was paid to have the consistency and physical state of the foods kept constant. This is an important factor in the use of test meals since Friedman and Pincus (10) have shown that a difference of as much as 32 per cent may exist in the gastric secretory response to a standard meat meal when the meat is ingested as ground beef or as small cubes.

The various foods of the two meals as well as the proportions of protein, fat, carbohydrate, and their caloric values are listed in tables 1 and 2. It will be noted that meal Type I (table 1) differed from meal Type II (table 2) mainly in that it contained beef-broth and fish rather than cottage cheese and cream pea-soup as the main source of protein. However, the total protein content and carbohydrate content were practically identical in both meals. The presence of whitefish in meal Type I resulted in a somewhat higher caloric value, due mainly to the high fat content of the fish.

Aspiration of Gastric Contents. Three series of experiments were performed. In Series I the subjects were permitted their usual noon meal but were not permitted any other food thereafter. At 6 p.m. the stomach of each individual was completely emptied by aspiration. Very shortly after aspiration the subject was given an evening meal of Type I. Thereafter, from 8 p.m. until 12 midnight, small hourly

samples of gastric contents were withdrawn for purpose of determining the free and total acidity. At 12 midnight and once hourly afterward until 8 a.m. the stomach

TABLE 1
Meal with beef broth and fish

	GRAMS	PROTEIN	FAT	CARBOHYDRATE	CALORIES
Bouillon (beef broth).....	100	1.0			4
Soda crackers.....	10	0.9	0.9	7.3	42
Broiled whitefish.....	120	27.5	7.8		180
Slice lemon.....	20	0.2	0.1	1.8	9
Mashed potatoes.....	100	2.0	0.1	19.0	85
Butter.....	10	0.1	8.5		77
Strained orange juice.....	200	1.2		26.2	110
Vanilla ice cream.....	50	1.3	3.4	5.6	58
White bread.....	40	3.6	0.8	20.8	104
Butter.....	10	0.1	8.5		77
20% cream and coffee.....	25	0.6	4.6	4.1	48
Sugar.....	15			15.0	60
Milk.....	200	6.6	8.0	10.0	138
Total.....		45.1	42.7	109.8	992

TABLE 2
Meal without beef broth or fish

	GRAMS	PROTEIN	FAT	CARBOHYDRATES	CALORIES
Cream pea soup					
Flour.....	5	0.5	0.1	3.8	18
Purée fresh peas.....	50	3.4	0.2	0.9	51
Milk.....	100	3.3	4.0	5.0	69
Soda crackers.....	10	0.9	0.9	7.3	42
Cottage cheese.....	120	23.0	1.0	4.8	120
Mashed potatoes.....	100	2.0	0.1	19.0	85
Butter.....	10	0.1	8.5		77
Vanilla ice cream.....	50	1.3	3.4	5.6	58
White bread.....	40	3.6	0.8	20.8	104
Butter.....	10	0.1	8.5		77
20% cream and coffee.....	25	0.6	4.6	4.1	48
Sugar.....	20			20.0	80
Grapefruit juice.....	100	0.6	0.2	12.0	52
Total.....		39.4	32.3	103.3	881.

was completely aspirated. This series included 19 studies on 7 normal young men, 15 studies on 8 normal young women and 21 studies on 7 young men with uncomplicated duodenal ulcer.

In experiments of Series II the procedure was as in Series I with this important exception: The meal designated Type I was given the subject at noon and a different meal, Type II was allowed at 6 p.m. As will be seen from tables 1 and 2, these meals differed mainly in that Type II did not contain the meat extractives (beef broth) and fish present in Type I. These substances are known to be powerful gastric secretagogues and we sought to determine whether their exclusion from the evening meal would decrease the volume and acidity of the nocturnal gastric secretion. This series included 21 studies on the aforementioned 7 ulcer patients.

In experiments of Series III the subjects were given meal Type I at 6 p.m. The stomach was then completely emptied by aspiration at 12 midnight. From 12 midnight until 7 a.m. the stomach was aspirated continuously by suction applied to the indwelling gastric tube. By this technique the entire gastric contents were constantly being removed throughout the night rather than at hourly intervals as in

TABLE 3
High peaks of free acid concentration (clinical units) in each of the night secretion studies

SECRESSION STUDIES ON	TOTAL STUDIES	HIGH PEAK FOR EACH OF THE NIGHT STUDIES												No. OVER 60 CLINICAL UNITS	No. OVER TO CLINICAL UNITS	No. OVER 60 CLINICAL UNITS					
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%								
Normal males	19	32	37	38	48	54	58	61	68	68	75	80	81	85	87	95	96	105			
Normal females	15	22	24	35	42	44	52	59	59	65	73	78	78	87	88	93	7	47			
Ulcer patients (see table 1 for meal at 6 p.m.; includes beef broth and fish)	21	29	30	40	50	56	56	58	58	60	60	61	61	63	64	68	75	82	85	93	
Ulcer patients (see table 1 for meal at 12 noon; see table 2 for meal at 6 p.m.; beef broth and fish included at noon meal only)	21	8	30	35	36	42	44	50	54	56	56	60	60	64	68	70	72	72	74	76	80
																11	52	7	33	1	5

the other two series of experiments. This series included 39 studies on 23 normal men and 35 studies on 22 male duodenal ulcer patients.

Laboratory. The volume of each sample of gastric contents was measured and the free and total acidity determined by titration with 0.01 normal sodium hydroxide, using Topfers reagent and phenolphthalein as indicators. Note was made of the presence or absence of mucus, bile, blood, and food residues.

Results

The data obtained in this investigation are summarized in tables 3 to 9 inclusive and Charts I to VII inclusive. While the practical and more clinical aspects of these studies have been discussed by us in detail elsewhere (1), the following conclusions pertinent to the problems under consideration in the present paper may be stated briefly:

(1) Both normal persons and patients with duodenal ulcer secrete acid gastric juice during the night.

TABLE 4

The minimum, maximum and average volumes (in cubic centimeters) obtained during the eight nocturnal aspirations in each of the series of subjects

	MINIMUM VOLUME (HOURLY ASPIRATION)	MAXIMUM VOLUME (HOURLY ASPIRATION)	AVERAGE VOLUME
Normal males.....	61	209	124
Normal females.....	75	269	184
Ulcer patients (see table 1 for meal at 6 p.m.; includes beef broth and fish).....	57	664	224
Ulcer patients (see table 1 for meal at 12 noon; see table 2 for meal at 6 p.m.; beef broth and fish included at noon meal only).....	40	451	209

TABLE 5

Volumes (in cubic centimeters) aspirated during the eight hourly aspirations (1 a.m. to 8 a.m.)

SECRETION STUDIES ON	TOTAL STUDIES	UNDER 100 CC.	100 TO 150 CC.	150 TO 200 CC.	200 TO 300 CC.	300 TO 400 CC.	400 TO 500 CC.	500 TO 600 CC.	600 TO 700 CC.	300 CC. OR OVER
Normal males.....	19	7	7	3	2	0	0	0	0	0
Normal females.....	15	1	3	5	6	0	0	0	0	0
Ulcer patients (see table 1 for meal at 6 p.m.; includes beef broth and fish).....	21	5	3	3	5	2	2	0	1	5 (24%)
Ulcer patients (see table 1 for meal at 12 noon; see table 2 for meal at 6 p.m.; beef broth and fish included at noon meal only).....	21	5	5	3	2	3	3	0	0	6 (28%)

TABLE 6

The total output of free hydrochloric acid (expressed as milligrams of hydrochloric acid) for eight hourly aspirations (12 midnight to 8 a.m.)

SECRETION STUDIES ON	TOTAL STUDIES	0-49 MG. HCl	50-99 MG. HCl	100- 199 MG. HCl	200- 299 MG. HCl	300- 399 MG. HCl	400- 499 MG. HCl	500- 599 MG. HCl	600- 699 MG. HCl	700- 799 MG. HCl	800- 899 MG. HCl	300 MG. HCl OR OVER
Normal males.....	19	4	3	4	4	3	1	0	0	0	0	4 (21%)
Normal females.....	15	2	4	6	1	1	1	0	0	0	0	2 (13%)
Ulcer patients (see table 1 for meal at 6 p.m.; includes beef broth and fish).....	21	5	2	5	0	4	3	0	1	0	1	9 (43%)
Ulcer patients (see table 1 for meal at 12 noon; see table 2 for meal at 6 p.m.; beef broth and fish included at noon meal only).....	21	9	1	3	6	0	1	1	0	0	0	2 (10%)

(2) Following a fairly well balanced meal at 6 p.m. (which included beef broth and fish—see table 1) the nocturnal gastric juice from patients with uncomplicated duodenal ulcer is on the average approximately of the same acid concentration as is the gastric juice from normal subjects of the same sex (see Chart I and table 3).

(3) When *intermittent single aspirations* are performed during the night (*not continuous aspirations*) a greater quantity of gastric juice can be withdrawn from the stomach of the duodenal ulcer patient than from the stomach of the normal subjects of the same sex (see Chart VII and tables 4-7).

(4) Following this meal at 6 p.m. (see table 1), the nocturnal volume of gastric juice in patients with uncomplicated duodenal ulcer, *as obtained by continuous*

TABLE 7
Volumes (in cubic centimeters) aspirated at 12 midnight

SECRETION STUDIES ON	NO. OF STUDIES	1 TO 40 CC.	41 CC. TO 60 CC.	61 CC. TO 80 CC.	81 CC. TO 100 CC.	OVER 100 CC.	AVERAGE VOLUME, CC.*	60 CC. OR OVER
Normal males.....	19	16	2	1	0	0	27	1-5.2%
Normal females.....	15	12	2	1	0	0	28	1-6.6%
Ulcer patients (see table 1 for meal at 6 p.m.; includes beef broth and fish).....	21	10	3	3	2	3	51	8-38%
Ulcer patients (see table 1 for meal at 12 noon; see table 2 for meal at 6 p.m.; beef broth and fish included at noon meal only).....	21	10	4	4	2	1	45	7-33%

* The volumes aspirated at 12 midnight in these studies are less than those shown in tables 8 and 9 because samples were also obtained for titration at 8, 9, 10 and 11 p.m.

suction, is on the average not greater than that of normal subjects of the same age and sex (tables 8 and 9).

(5) When the noon meal (instead of the evening meal) includes meat and fish broth as a source of protein (for diets see tables 1 and 2) the stomach contains less free hydrochloric acid during the night (see table 6).

(6) Composite curves based on the average hydrochloric acid concentration may be misleading. A peak in the concentration of acid during the night in one subject may be offset by a low concentration in another subject (or in the same subject on another night). We therefore present several graphs which we found to represent certain patterns. (See Patterns 1, 2, 3 and 4—Charts 2, 3, 4 and 5.)

(7) The nocturnal curves of free hydrochloric acid concentration vary considerably. Not only is there variation from one normal person to another and from one ulcer patient to another, but also variations in the same individual on

TABLE 8
Volume of gastric juice by continuous suction from 12 midnight to 7 a.m.
 Normal Male Subjects

NO. OF STUDY	CASE	DATE OF STUDIES	VOLUME IN CC. ASPIRATED AT 12 MIDNIGHT	VOLUME, 12 TO 7 A.M. IN CC.	FREE ACID, CLINICAL UNITS	TOTAL ACID, CLINICAL UNITS	FREE ACID, MG. HCl
1	1	12/17/42	10	433	35	45	553.2
2	2	12/16/42	33	591	68	76	1,466.9
3	3 a	12/15/42	6	190	10	30	69.4
4	b	12/16/42	76	326	70	80	832.9
5	c	12/18/42	95	256	26	36	242.9
6	d	12/21/42	16	315	10	24	115.0
7	4 a	12/15/42	15	507	75	100	1,387.9
8	b	12/16/42	42	647	86	90	2,030.9
9	c	12/18/42	26	610	84	90	1,870.3
10	d	12/21/42	15	486	86	94	1,525.6
11	5 a	12/15/42	55	507	62	76	1,147.3
12	b	12/17/42	20	240	48	76	420.5
13	c	12/18/42	50	245	62	78	554.4
14	d	12/21/42	40	331	76	86	918.2
15	6 a	12/15/42	60	299	2	16	21.8
16	b	12/17/42	15	277	10	16	101.1
17	7	11/17/43	70	375	60	80	821.3
18	8	11/17/43	200	495	0	12	0
19	9	11/17/43	140	460	0	18	0
20	10 a	1/20/44	145	330	25	54	301.1
21	b	1/26/44	110	340	29	60	359.9
22	11 a	1/20/44	70	205	0	26	0
23	b	3/22/44	195	220	22	44	156.7
24	12 a	1/20/44	60	560	11	29	224.8
25	b	1/26/44	70	390	18	39	256.2
26	c	3/22/44	170	790	60	80	1,730.1
27	13	1/20/44	80	*	*	*	*
28	14	1/20/44	290	*	*	*	*
29	15 a	1/26/44	205	480	0	15	0
30	b	3/22/44	150	565	23	40	474.3
31	16 a	1/26/44	80	210	6	35	46.0
32	b	3/22/44	75	660	58	78	1,397.2
33	17	1/26/44	160	560	23	43	470.1
34	18	3/22/44	100	650	15	34	355.9
35	19	11/16/44	60	400	23	45	335.8
36	20	11/16/44	160	550	23	40	461.7
37	21	11/16/44	140	600	40	66	876.0
38	22	11/16/44	180	800	6	28	175.2
39	23	11/16/44	150	600	28	58	613.2
Total.....			3,634	16,500			22,313.8
Average.....			93†	446			603

* Incomplete data.

† The average volume of gastric contents aspirated at midnight in these cases is higher than the average volume aspirated in the cases shown in table 7 because in the latter subjects samples were obtained hourly from 7 p.m. to 12 midnight for titration.

TABLE 9
Volume of gastric juice by continuous suction from 12 midnight to 7 a.m.
 Male Duodenal Ulcer Patients

NO. OF STUDY	CASE	DATE OF STUDIES	VOLUME IN CC. ASPIRATED AT 12 MIDNIGHT	VOLUME 12 TO 7 A.M. IN CC.	FREE ACID, CLINICAL UNITS	TOTAL ACID, CLINICAL UNITS	FREE ACID, MG. HCl
1	1 a	7/18/43	160	263	16	44	153.5
2	b	7/24/43	100	155	10	42	56.5
3	c	7/25/43	150	170	24	46	148.9
4	2 a	7/24/43	170	1,143	98	114	4,088.5
5	b	11/ 6/43	340	1,130	80	100	3,299.6
6	c	11/10/43	330	350	55	75	702.6
7	d	12/ 1/43	390	1,310	40	73	1,912.6
8	3 a	7/10/43	40	501	8	32	146.3
9	b	7/12/43	23	290	44	58	465.7
10	c	1/11/44	180	560	3	27	61.3
11	4 a	7/18/43	10	225	20	40	164.2
12	b	7/25/43	10	808	6	18	176.9
13	5 a	7/10/43	50	221	50	78	403.3
14	b	7/24/43	70	299	54	78	589.3
15	6	11/ 6/43	475	320	90	110	1,051.2
16	7 a	11/ 6/43	380	390	20	50	284.7
17	b	11/10/43	400	440	20	40	321.2
18	8	11/10/43	400	740	0	10	0
19	9	1/11/44	110	430	0	32	0
20	10	1/11/44	410	710	60	90	1,554.9
21	11 a	12/ 1/43	190	260	5	25	47.4
22	b	1/11/44	220	470	30	66	514.6
23	12	6/26/43	500	409	14	32	209.0
24	13	1/11/44	110	440	19	33	305.1
25	14 a	5/18/45	120	520	75	102	1,423.5
26	b	5/23/45	110	800	86	135	2,511.2
27	c	6/ 2/45	210	820	59	71	1,722.8
28	15	5/23/45	90	120	50	74	219.0
29	16	5/23/45	130	240	15	39	131.4
30	17	5/24/45	100	585	48	84	1,024.9
31	18	5/24/45	240	240	37	52	324.1
32	19	5/24/45	190	240	31	47	271.6
33	20	5/30/45	100	290	37	48	391.7
34	21	5/30/45	80	765	65	77	1,815.0
35	22	6/ 2/45	60	350	45	57	574.9
Total.....			6,648	16,972			27,067.4
Average.....			190*	485			773.3
Average excluding case 2.....			160*	383			501.9

* The average volume of gastric contents aspirated at 12 midnight in these cases is higher than the average volume aspirated in the cases shown in table 7 because in the latter subjects samples were obtained hourly from 7 p.m. to 12 midnight for titration.

different nights, even though the conditions as to the nature of the meal, consistency of the food, time of eating, etc., have been kept constant.

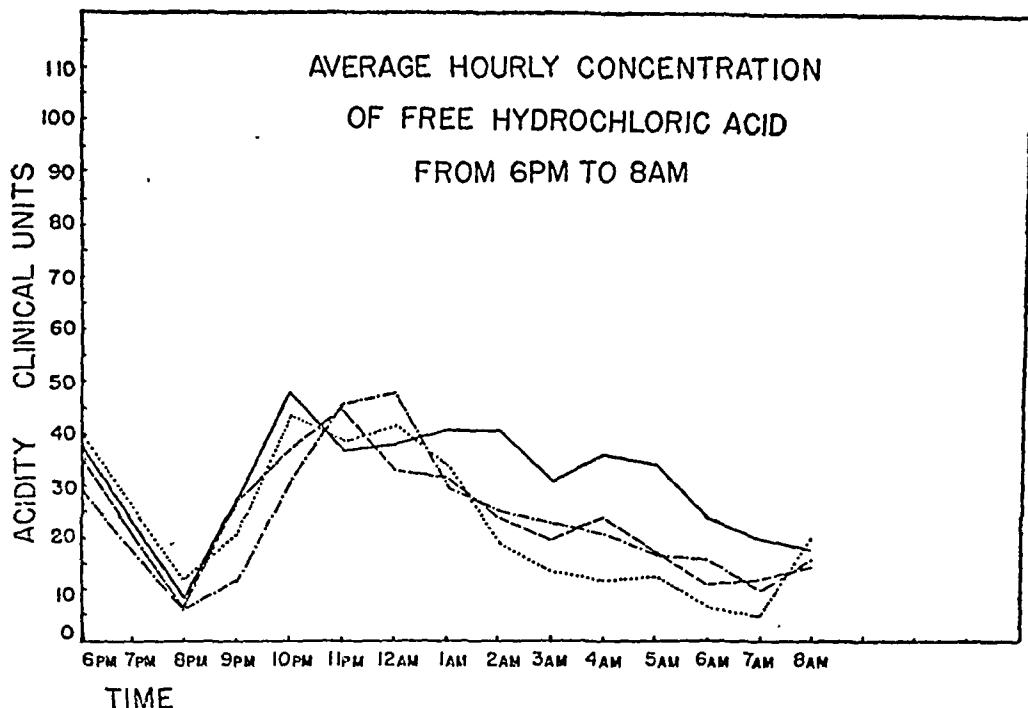


CHART 1. AVERAGE HOURLY CONCENTRATION OF FREE HYDROCHLORIC ACID FROM 6 P.M. TO 8 A.M.

Solid line, normal males, 19 studies; for type of meal at 6 p.m. see table 1. Broken line, normal female, 15 studies; for type of meal at 6 p.m. see table 1. Line of dashes and dots, ulcer (duodenal) patients, 21 studies; for type of meal at 6 p.m. see table 1. Dotted line, ulcer (duodenal) patients, 21 studies; for type of meal at 12 noon see table 1, and for type of meal at 6 p.m. see table 2.

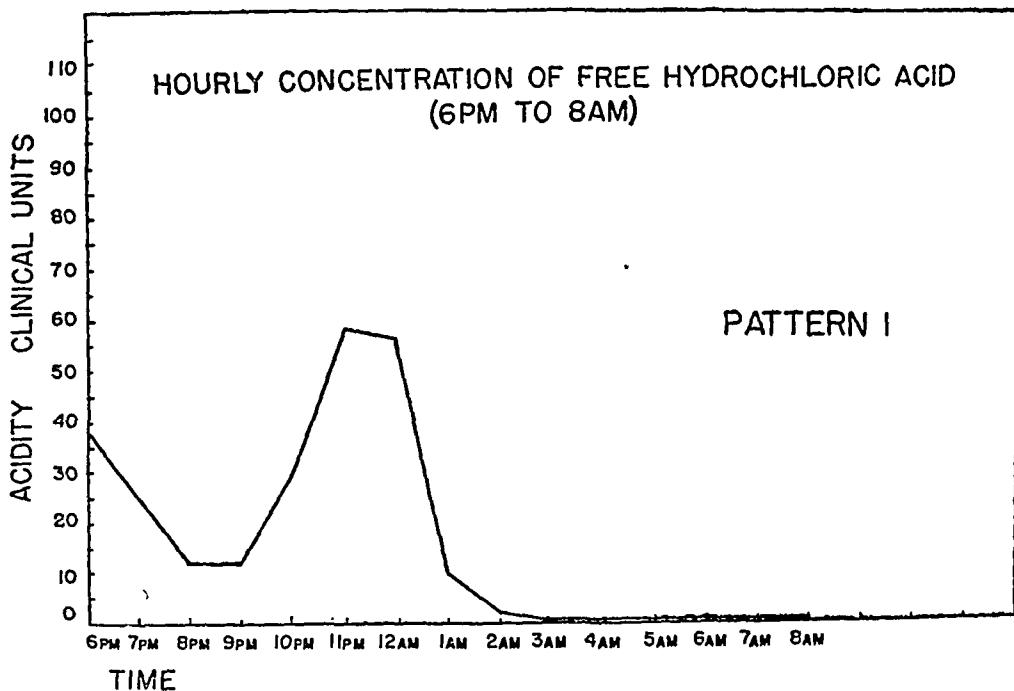


CHART 2. (MR. B., DUODENAL ULCER), PATTERN 1 IN HOURLY CONCENTRATION OF FREE HYDROCHLORIC ACID FROM 6 P.M. TO 8 A.M.

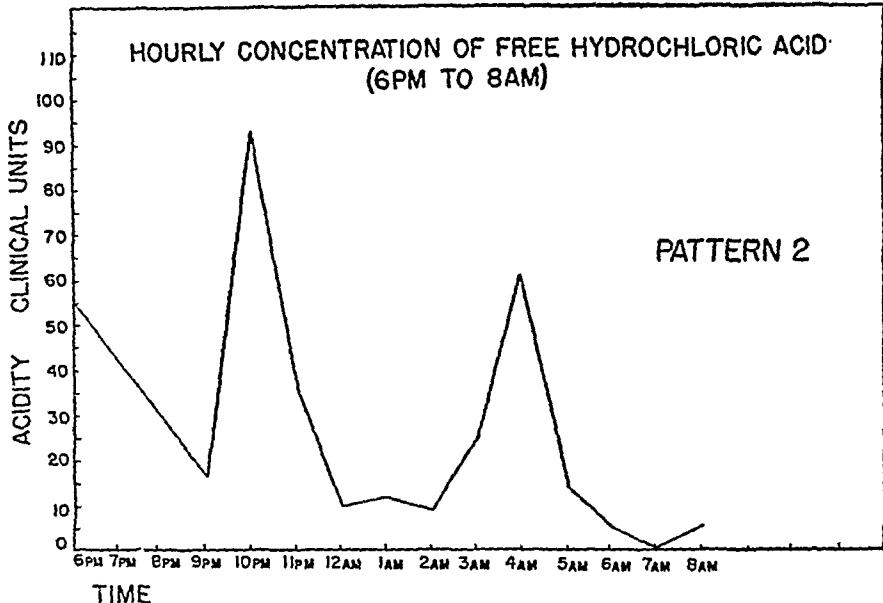


CHART 3. (MISS H., NORMAL FEMALE), PATTERN 2 IN HOURLY CONCENTRATION OF FREE HYDROCHLORIC ACID FROM 6 P.M. TO 8 A.M.

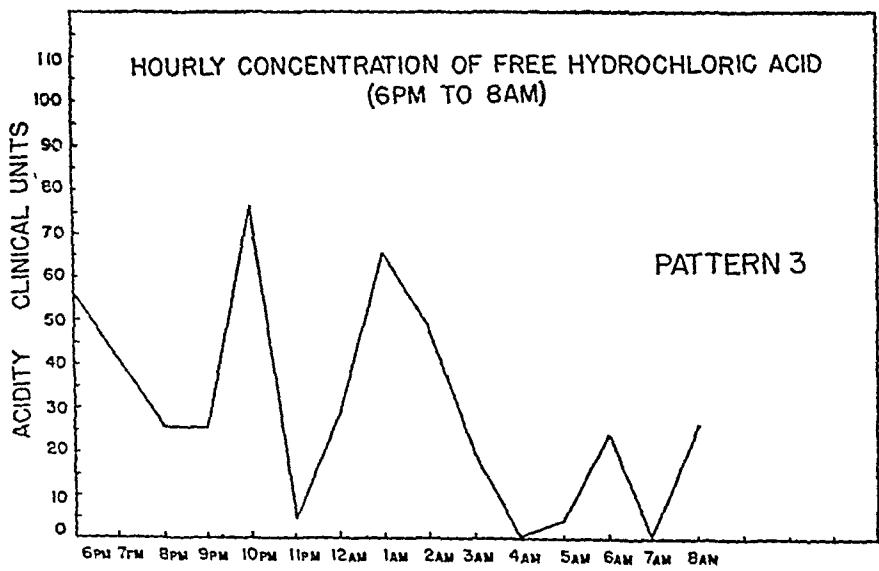
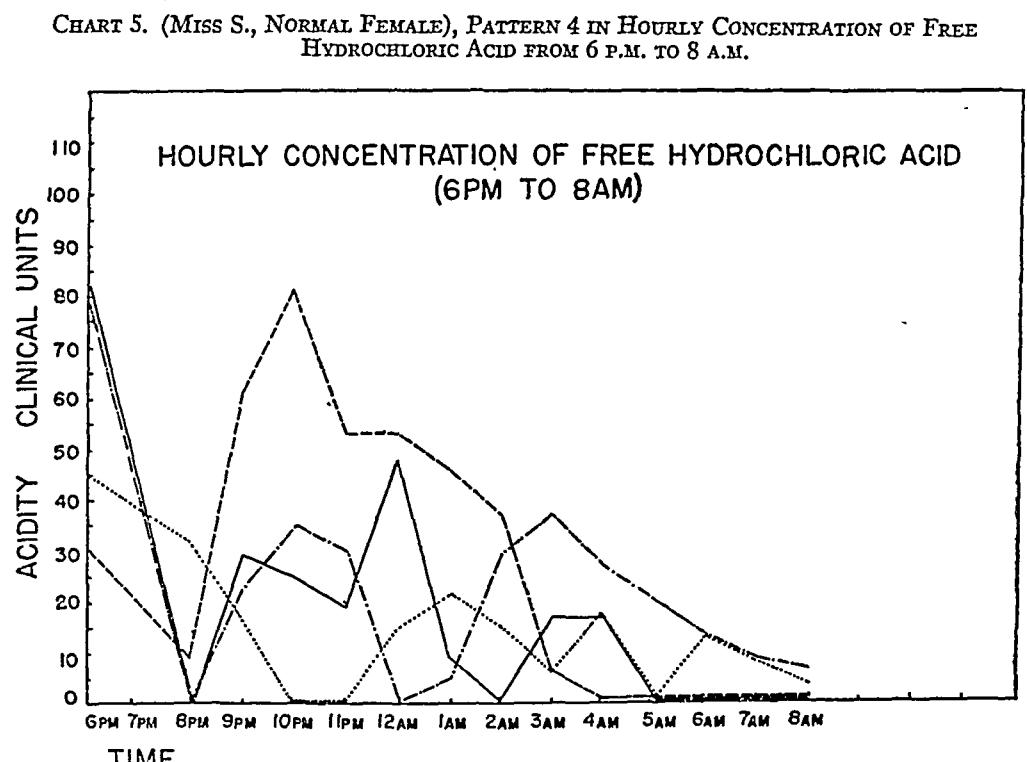
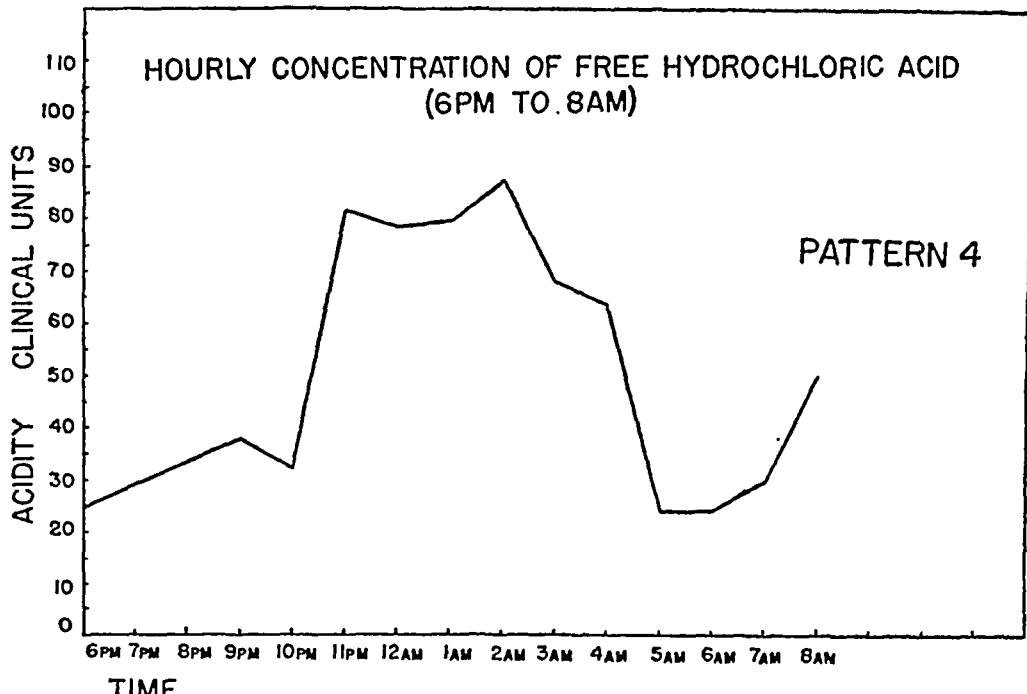


CHART 4. (MR. O. R., DUODENAL ULCER), PATTERN 3 IN HOURLY CONCENTRATION OF FREE HYDROCHLORIC ACID FROM 6 P.M. TO 8 A.M.



Broken line, Feb. 25, 1940; dotted line, Mar. 3, 1940; line of dashes and dots, Mar. 6, 1940; solid line, Mar. 10, 1940. Nocturnal curved of free hydrochloric acid concentration vary considerably. They vary not only from one subject to another, but also in the same subject on different nights, as seen in this graph.

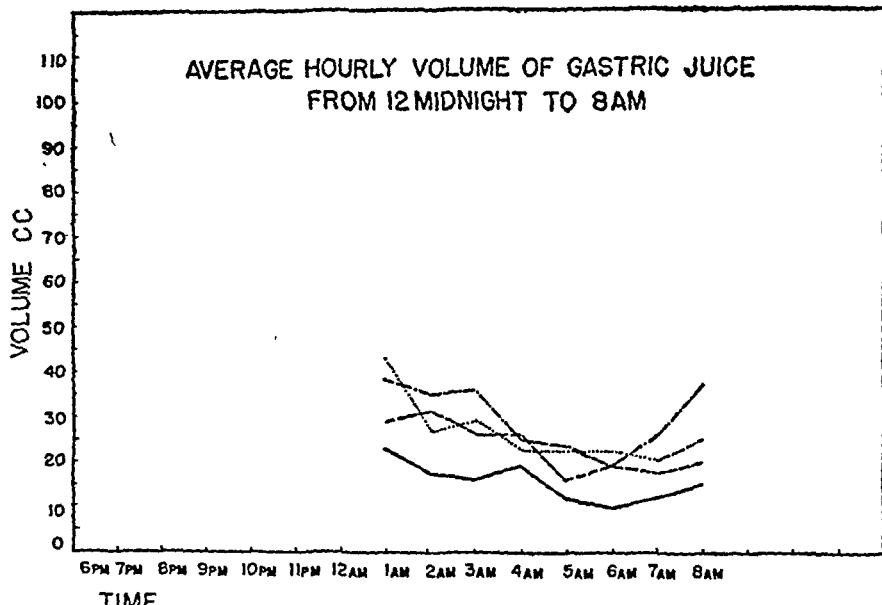


CHART 7. AVERAGE HOURLY VOLUME OF GASTRIC JUICE FROM MIDNIGHT TO 8 A.M.

Solid line, normal males, 19 studies; for type of meal at 6 p.m. see table 1. Broken line, normal female, 15 studies; for type of meal at 6 p.m. see table 1. Line of dashes and dots, ulcer (duodenal) patients, 21 studies; for type of meal at 6 p.m. see table 1. Dotted line, ulcer (duodenal) patients, 21 studies; for type of meal at 12 noon see table 1, and for type of meal at 6 p.m. see table 2.

Comments

(1) Our results confirm in general those of several other investigators who found that in normal healthy humans there is a continuous nocturnal gastric secretion. To what extent this nocturnal secretion in our subjects was spontaneous in origin we do not know since all experiments were carried out after the feeding of a standard meal at 6 p.m. Any spontaneous activity of the gastric glands would of course be masked by the secretory effect of the food, at least during the earlier part of the night. Probably much of the secretion after midnight could be designated as that of the "intestinal phase" since complete aspiration of the stomach at this time revealed that nearly all of the food had passed into the intestine. This so-called "intestinal phase" is of a complex nature and, according to Beamer, et al. (11), is dependent on several factors, including the presence of food and bile in the intestine.

(2) As determined by the method of intermittent hourly emptying of the gastric contents, it would appear that gastric secretion did not occur at a uniform rate throughout the night. The concentration of acid also varied from hour to hour. As Charts 2, 3, 4 and 5 show, the concentration of acid in the stomach could be plotted as falling into distinct pattern groups. The peak acidities after 3 a.m. shown in Charts 3 and 4 perhaps indicate spontaneous

secretory activity following cessation of secretion due to the food. However, this is frankly speculative. These graphs represent only the concentration of acid at regular intervals (hourly) and do not take into account possible dilution and neutralization by regurgitated intestinal contents or the effect of varying degrees of retention. However, it is nevertheless interesting to note that in most of the normal and ulcer subjects there occurred after 6 a.m. an increase in the volume of juice secreted (Chart 7). This increase coincided with the waking of the patient and probably represents a psychic secretion based on condition reflexes associated with the expectancy of eating breakfast. Presumably the juice secreted during this period is what one finds on aspirating the stomach before breakfast.

✓(3) Perhaps the most significant point in our study was the finding that by continuous aspiration of the gastric contents there was *no difference between normal subjects and patients with uncomplicated duodenal ulcer as regards the volume and acidity of the gastric juice secreted throughout the night.* In this respect we are in disagreement with the conclusions drawn by several other investigators that patients with duodenal ulcers tend to show a hypercontinuous gastric secretion. Several possible explanations suggest themselves.

Most of the other investigators appear to have studied gastric secretion in their ulcer patients while they were presenting acute active ulcer symptoms. Their patients were so acutely ill that they required hospital management. A number of their patients might have had "intractable" ulcers with or without complications. However, our patients were all ambulatory and had only mild distress at the time of our study. They all presented *uncomplicated* duodenal ulcer. They were the average run of ulcer patients one sees in a large office practice. In addition, we were extremely careful in the selection of a normal group of subjects as our control series.

It is the consensus of other workers that the patient suffering acute ulcer pains does exhibit a true hypersecretory state. We have seen several such patients, particularly those presenting intractable ulcer clinically, usually with (though occasionally without) complications. The reason for hypersecretion in these cases is unknown. Babkin (12) pointed out numerous conditions in which an apparently spontaneous gastric secretion could in fact be due to *psychic* and somatic reflexes as well as chemical substances and infections.

✓(4) As stated above, both the volume and concentration of acid of the gastric juice aspirated by continuous suction during the night are no greater in patients with uncomplicated duodenal ulcer than in normal healthy subjects. However, by consecutive hourly aspirations of the stomach it was found that the stomach of the ulcer patient contains more of the juice that it secretes than does the stomach of the normal subject. This may be indicative of a greater degree of retention by the ulcer patient's stomach. The reason for the retention, if

such is actually present, is unknown but reflexes originating in the intestine may play a role. As Thomas (13) and Quigley (14) and their co-workers have shown, the pyloric sphincter functions mainly as a mechanism to prevent regurgitation from the intestine. According to these workers gastric evacuation is largely dependent on the existence of an intraluminal pressure gradient between the stomach and duodenum. The pyloric sphincter may be relaxed for long periods of time without gastric emptying occurring if the pressure within the lumen of the pyloric antrum does not exceed the pressure within the lumen of the duodenum. Acid and other substances placed in the intestine will result in closure of the pyloric orifice, a point perhaps pertinent to the present discussion. Reflexes from the rectum, colon, small bowel and urinary bladder (15, 16, 17, 18) have been shown to inhibit gastric tonus and motility under certain conditions. The possibility should also be considered that in the ulcer patient there is impairment of the mechanism regulating gastric secretion through the effect of a low intestinal pH. (18a). However more experimental data must be obtained to support this interesting viewpoint.

(5) It is of interest to note that the 2 ulcer patients (table 9, cases 2 and 14) in whom we found a total of 2,500 mg. or more of hydrochloric acid during the seven-hour period of the night have been suffering from more or less intractable ulcers clinically, though no complicating factors were found on physical or roentgen examinations. During the last three years each of these patients has had shorter symptom-free intervals and longer periods of ulcer distress and both are responding now less favorably to medical management. It is possible that the hydrochloric acid output in milligrams during the night is of greater clinical significance than the volume of secretion alone or the concentration of hydrochloric acid alone. We are studying this problem further.

(6) Strict comparison of the results obtained in our study with those obtained by other investigators is not possible since each of the investigations were carried out under different conditions. Thus, factors such as the composition, amount and consistency of the test meal, the time of ingestion of the meal, the time of aspiration of the gastric contents, etc., are not constant in all studies. These variations would naturally affect the volume and acidity of the gastric samples, making comparison of the various data unreliable.

✓(7) Alvarez, Vanzant and Osterberg (19) and Ruffin and Dick (20) have shown that wide variations may be found in the concentration of acid following an Ewald test meal and histamine injections respectively. Their studies were conducted during the day. Our studies, conducted during the night (following a meal at 6 p.m.), likewise show wide variations.

(8) It is conceivable that the Levine tube which remained in the stomach during the night acted as an excitatory or an inhibitory stimulus on gastric secretion. Since our studies dealt primarily with comparative results in 4

different studies, presence of the tube is a "constant" factor throughout the study, and its influence does not enter into the problem. However, it is interesting that Chalfen (3) found that the introduction of a tube for aspiration has no effect on either the volume or the acidity of the secretion.

(9) It is a well known fact that at times one observes some patients with duodenal ulcer from whom 500 cc. or more of gastric juice may be aspirated around 1 or 2 a.m. We have 1 such sample in our series (case 2, table 9). If the results of this 1 ulcer patient are eliminated from the averages in table 9 the average nocturnal output of hydrochloric acid in milligrams is slightly less for the ulcer patients than for the normal subjects of the same sex.

When these data are analyzed statistically the difference between the normal subjects and patients with duodenal ulcer are not significant.

(10) The only other report we were able to find on comparative nocturnal gastric secretion in normal subjects and ulcer patients by means of continuous suction is that of Mears (7). Working primarily on the effect of atropine on gastric secretion during the night, he performed 1 control study on each of his subjects during one night and during the next night conducted a similar study with atropine. He found that the secretory rate, the volume of secretion and the free and total acidity are higher for the ulcer group. His studies, however, differ from ours in the following major points:

(a) His normal or control group comprised "50 University Hospital patients who presented no evidence of gastro-intestinal disease other than chronic cholecystitis and recurrent appendicitis in the interval phase." His ulcer patients consisted of "15 (hospital) patients with active duodenal ulcer." Our ulcer patients were ambulatory subjects and presented only mild distress. They did not present the acute illness that warranted hospitalization. What is more important, however, is the fact that our normal group were medical students and interns who were selected for study because they were free from any illness of any type. It is well known that patients with chronic cholecystitis, especially those ill enough to be hospitalized for medical or surgical management, have a lower volume of gastric juice and a lower acidity than normal subjects. Patients with chronic appendicitis may also present an abnormal gastric secretion. While these differences may not affect the accuracy of Mears' comparative studies on the effect of atropine, his findings on "normal" subjects may be questioned.

(b) The normal group studied by Mears consisted of 30 women and 20 men; the ulcer group comprised 13 males and 2 females. Our studies by means of continuous suction compare results in subjects of the same sex (all males). The preponderance of females in the normal group of Mears (60 per cent) and the negligible number of females in his ulcer group (13 per cent) may also play a part in the difference of results.

(c) In his studies the meal was given at 5 p.m. and continuous suction was started at 7 p.m. (two hours after the meal) while in our studies the meal was given at 6 p.m. and the stomach was not aspirated until 12 midnight. Our comparative results on night secretion, therefore, include not only the complete gastric (or chemical) phase of secretion but also the intestinal phase of gastric secretion. In our patients the affects on gastric secretion of food in the intestine were manifested, (11) since complete emptying of the stomach by aspiration was not carried out until six hours after ingestion of the meal. By this time all the food had already passed into the intestine. On the other hand, in the patients studied by Mears, aspiration was started two hours after the meal, and thus very little passed into the intestine. In his subjects food remained in the stomach only two hours.

The difference in the two studies may at least in part explain the differences in results and serve to emphasize the need for additional studies on nocturnal gastric secretion on both normal subjects and ulcer patients by the continuous aspiration method.

CONCLUSIONS

(1) Following a fairly well balanced meal at 6 p.m. (see table 1) a normal person secretes acid gastric juice during the night. By means of continuous suction, an average of 446 cc. of gastric juice was obtained from 12 midnight to 7 a.m. (minimum 190 cc.; maximum 800 cc.).

(2) There is no statistically significant difference in the volume and total output of acid of nocturnal gastric secretion of normal subjects and patients with uncomplicated duodenal ulcer when determined by continuous aspiration.

(3) The greater volume of gastric juice observed when intermittent single aspirations are made from patients with uncomplicated duodenal ulcer is not due to gastric hypersecretion.

REFERENCES

- (1) SANDWEISS, D. J., SUGARMAN, M. H., PODOLSKY, H. M., AND FRIEDMAN, N. H. F.: *J. A. M. A.*, 130: 258, 1946.
- (2) BEAUMONT, W.: *Burlington*, 1837.
- (3) CHALFEN, S. S.: *Arch. f. Verdauungskr.*, 44: 250, 1928.
- (4) WINKELSTEIN, ASHER: *Am. J. Digest. Dis.*, 1: 778, 1935.
- (5) CORNELL, A., WINKELSTEIN, A., AND HOLLANDER, F.: *Bull. New York Acad. Med.*, 20: 413 1944.
- (6) VAL DEZ, F. C.: *Illinois M. J.*, 81: 149, 1942.
- (7) MEARS, F. B.: *Surgery*, 13: 214, 1943.
- (8) HENNING, N., AND NORPOTH, L.: *Arch. f. Verdauungskr.*, 53: 64, 1933.
- (9) HELLEBRANDT, FRANCES A., TEPPER, RUBY E. H., GRANT, HELEN AND CATHERWOOD, RUTH: *Am. J. Digest. Dis.*, 3: 477, 1936.
- (10) FRIEDMAN, M. H. F., AND PINCUS, I. J.: *Exper. Med. & Surg.*, 3: 100, 1945.
- (11) BEAMER, W. D., FRIEDMAN, M. H. F., THOMAS, J. E., AND REHFUSS, M. E.: *Am. J. Physiol.*, 141: 615, 1944.

- (12) BABKIN, B. P.: Libman Anniv. Vol. 1: 113, 1932.
- (13) THOMAS, J. E.: Rev. Gastroenterology 2: 32, 1935.
- (14) QUIGLEY, J. P.: "Med. Physics" Edited by Glasser O. 1944.
- ✓(15) LOWE, E. R., AND PATTERSON, T. L.: Quart. J. Exp. Physiol. 28: 305, 1938.
- ✓(16) PATTERSON, T. L., AND DUNN: Proc. Am. Phys. Soc. p. 222, 1941.
- ✓(17) PATTERSON, T. L., AND SANDWEISS, D. J.: Am. J. Digest. Dis., 9: 375, 1942.
- ✓(18) PATTERSON, T. L., AND SANDWEISS, D. J.: Federation Proceed. 3: 36, 1944.
- (18a) PINCUS, I. J., THOMAS, J. E., AND REHFUSS, M. E.: Proc. Soc. Exp. Biol. and Med. 51: 367, 1942; SHAY, H., GERSHON-COHEN, J., AND FELS S.: Am. J. Digest. Dis., 9: 124, 1942; PINCUS, I. J., FRIEDMAN, M. H. F., THOMAS, J. E., AND REHFUSS, M. E., Am. J. Digest. Dis., 11: 205, 1944.
- (19) ALVAREZ, WALTER C., VANTZANT, FRANCES R., AND OSTERBERG, ARNOLD E.: Am. J. Digest. Dis., 3: 162, 1936.
- (20) RUFFIN, JULIAN M., AND DICK, MACDONALD: Ann. Int. Med., 12: 1940, 1939.

COMPLICATIONS OF CHRONIC NON-SPECIFIC ULCERATIVE COLITIS

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INTRODUCTION

The complications of chronic, non specific ulcerative colitis, an inflammatory disease of unproved etiology, have been studied by various workers. Jackman, Bargen and Helmholz (1), in careful statistical analysis found complications present in children in 47.4 per cent whereas in the entire group 871 children and adults the incidence was 41 per cent. On the other hand multiple complications were considerably greater for the whole group, 15.2 per cent, than they were in children, 9.5 per cent. Schlicke and Bargen (2) have compared the complications in a similar number of surviving and fatal cases of the fulminating type. Chronic perforation occurred in six of the first group and in one of the second.

The purpose of this paper is to review the experience of the University of Chicago Clinics with respect to the complications of ulcerative colitis.

DIAGNOSIS

The diagnosis of chronic non-specific ulcerative colitis was based primarily upon the presence of the typical proctoscopic picture as indicated in the following table:

	No. of Cases	Percentage
Examination not recorded.....	10	4.85
Typical changes in the rectal mucosa.....	193	93.68
Normal rectal mucosa with roentgenologic evidence of disease of the transverse and descending portions of the colon.....	3	1.45
Total.....	206	

The alterations in the rectal mucosa in the 193 cases consisted of friability, granularity, edema, superficial ulceration, and, in the healing phase, scarring. The usual routine examinations to exclude other diseases were made including x-ray examination of the chest, examination of the feces for parasites and pathogenic bacteria, Frei and complement neutralization tests in cases suggestive of lymphopathia venereum.

COMPLICATIONS

The 206 patients diagnosed as chronic non-specific ulcerative colitis between the opening of the institution late in 1927 and July 1945 may be divided into

142 (69 per cent) uncomplicated cases and 64 (31 per cent) complicated. The complications may be grouped and listed as follows:

	No. of Cases	Percentage
1. Complications arising from the local disease		
Polyps.....	21	10
Stricture.....	8	3.9
Obstruction.....	6	2.9
Carcinoma.....	3	1.4
Hemorrhage.....	13	6.8
2. Complications involving adjacent structures		
Fistula, internal or external.....		
Abscesses: peri-rectal, perianal, ischiorectal.....	9	4.4
Perforation.....	7	3.4
Peritonitis.....		
3. Complications distant from the colon		
Lesions of the skin or of the mucosal surfaces.....	22	10.67
Arthritis.....	12	5.82
Venous thrombosis.....	4	1.94
Hepatitis.....	1	0.48
Septic infections.....	27	13.10
4. Complications derived from deficient nutrition		
Malnutrition.....		
Infantilism (23 children).....	3	13.1
Avitaminosis.....		
5. Miscellaneous		

These complications will be discussed separately on the basis of their incidence, our experience with them, and references to the literature.

1. Colonic Complications

Polyps. The presence of polyposis in ulcerative colitis apparently was described first by Virchow (3) as colitis polyposa cystica. Bargen (4) in 1929 found it to be the most frequent complication of the disease, the incidence being 10 per cent. This is exactly the same as found in our series, using the proctoscopic examination as the basis for the diagnosis, 21 cases or 10 per cent. Late (5) differentiated the polyposis of ulcerative colitis from true polyposis, a differentiation Felsen (6) has recently emphasized. In ulcerative colitis the polyps may consist of islands of intact mucosa and hence are to be distinguished from adenomatous polyposis. In our opinion, this differentiation has no validity at all. It is true that many polyps are merely islands of mucosa more or less actively regenerating. Others exhibit various grades of metaplasia and indeed of neoplasia as will be discussed later under the heading of carcinomatous degeneration.

Stricture of the colon. Chronic inflammation of the colon tends toward rigidity and loss of elasticity producing a rather characteristic tube-like appearance. As the disease progresses the lumen diminishes in caliber and in some cases a

definite stricture is established. The stricture can occur at any point of the colon although the most frequent location is in the rectosigmoidal area. Bargen (4) found the incidence of stricture to be 8.5 per cent and Streicher (7) 7.4 per cent. In our series, using proctoscopic evidence only, stricture formation was noted in 3.88 per cent.

Obstruction of the colon. Occasionally the stricture is so marked that the bowel becomes obstructed. Lund (8) reported an instance of complete obliteration of the lumen. In our series six cases developed intestinal obstruction (2.91 per cent).

Carcinomatous degeneration. Carcinomatous degeneration is an uncommon occurrence (Ewing) (9). However, the constant destruction and repair produced by the inflammation and the rather high incidence of adenomatous polyps favor malignant degeneration (10). Bargen, 1928 (11), reported 23 cases with malignancy; in 14 of them carcinoma was proven, two had lymphosarcoma and one a lymphatic leukemia. In 1935 (12) he reported 25 additional cases, classifying six as grade 4 adenocarcinomas, one as grade 3, and five as grade 2. In younger patients a tendency to multiple carcinomatous degeneration and a higher grade of malignancy was noted. Recently Bargen and Sauer (13) reported another group of 30 cases, with multiple carcinomatosis. Granshorn (14) has shown that the carcinomatous changes are more frequent when hyperplasia of the mucous membrane is present. Chronic ulcerative colitis with carcinoma has been reported by several authors (15, 16). In one of our cases an 18 year old boy with infantilism and ulcerative colitis since the age of two and a half years was found at autopsy to have a carcinoma of the sigmoid also (17).

The incidence of carcinomatous transformation was found by Jackman, Bargen and Helmholz in a series of 871 adults to be 3.2 per cent and in 95 children, 6.3 per cent. Streicher (7) found an incidence of 1.2 per cent in 217 cases. In our series there were only three such instances, and incidence of 1.4 per cent.

Hemorrhage. The continuous loss of blood in the stools not infrequently produces a severe secondary anemia. Occasionally the feces appear to consist wholly of blood. Fatal hemorrhage has been reported (18, 19); in Bargen's (4) series the incidence was 0.04 per cent. The bleeding may be due entirely to the inflammatory and ulcerative process; other factors may be the lowered coagulability of the blood due to hypoprothrombenemia produced by a deficiency of vitamin K. This may result from defective absorption as well as defective storage. Page and Barcowitz (20) found that 6 (25.5 per cent) of 21 patients with chronic ulcerative colitis had a constant hypoprothrombenemia, 13 (61.9 per cent) could be classified as the borderline and only 2 (9.5 per cent) had a normal prothrombin clotting time. The administration of vitamin K in some cases reduces the bleeding.

Hemorrhoids. Hemorrhoids may constitute a very troublesome and even serious complication because of thrombosis or because of continued profuse bleeding. In our series they were noteworthy in 13 of the 206 cases—an incidence of 6.8 per cent.

2. Complications Involving Adjacent Structures

Abscesses and fistulae. Bargen (4) found perirectal abscesses in 3.7 per cent and Streicher (7) in four per cent; in this series there were nine cases, an incidence of 4.36 per cent. Perianal, perirectal and ischiorectal abscesses may drain externally or internally to an adjacent viscus or to the peritoneum producing peritonitis. Perianal fistulae are frequently intractable and may constitute an indication for ileostomy, perhaps followed by resection of the colon. In one of our cases a perianal abscess developed during penicillin and sulfonamide treatment.

External fistulae from the colon can open to the abdominal wall or the perianal region. The internal fistula can open to the small bowel, colon, stomach, gall bladder, bladder, duodenum, uterus, vagina. In the literature there are many reports on internal fistulae: colojejunogastric (21), cologastric and coloduodenal (22) rectovaginal (23). Bacteria isolated from such fistulae are non specific, both gram negative and gram positive organisms being present.

Perforation. Perforation and peritonitis are the most serious complications. Perforation can occur at a single place or in several places, although the latter is very unusual. Perforation is to be feared chiefly in fulminating cases or during acute exacerbations of the disease. Obstruction, of course, increases the likelihood of perforation (Bockus) (24). It may occur after ileostomy. Perforation may take place without any warning and at a time when the disease seems relatively quiescent. The symptoms may be typical with a sudden onset of sharp pain in the abdomen followed by peritonitis. In other cases, however, the onset is insidious and the clinical picture very atypical. In one case there was a history of mild abdominal pain of five days duration. A pneumoperitoneum was demonstrated roentgenologically when the patient was sent for a routine barium enema. In some instances the atypical picture is due in part to the extreme illness of the patient (25). Usually the perforation is walled off by the peritoneum or by adjacent structures; resulting in localized peritonitis, abscess, or fistula formation (24).

Bargen (4) found the incidence of perforation to be 2.6 per cent; Streicher (7), 1.2 per cent. In our series there were seven freee perforations, an incidence of 3.39 per cent. Bargen and Jacobs (26) reported 22 cases, 16 of which died, an incidence of 72.7 per cent.

Peritonitis. Generalized peritonitis is a dramatic and usually fatal complication, running a fulminating course as just described although atypical cases are seen. Palmer and Ricketts (28) described three cases of chronic

ulcerative colitis with signs of generalized peritonitis followed by recovery attributed primarily to therapy with sulfonamides and penicillin; although blood transfusions and other supportive measures were used. In one of these patients a laparotomy three weeks later disclosed the loops of the bowel bound together by the recent adhesions characteristic of peritonitis. The bacteria found in the peritoneum in cases of peritonitis complicating chronic ulcerative colitis is rich and varied consisting of aerobic and anaerobic organisms, gram negative bacilli and gram positive cocci of different types. Ungar (29) has shown a synergistic action of penicillin and sulfonamide in vitro and in vivo.

3. Complications Distant from the Colon

The exact cause of the complications distant from the colon is difficult to establish. The manifestations are quite varied, affecting the skin and mucosa surfaces, the joints, pleura, endocardium, liver, veins, etc.

Mouth, pharynx and larynx. Stomatitis may be very troublesome with multiple, large painful canker sores lining the cheeks, including the gums and tongue and extending down into the pharynx. In one of our cases the larynx was also involved producing not only a hoarseness of the voice but finally so much respiratory embarrassment that a tracheotomy became necessary. This afforded prompt relief. In a few days the inflammation subsided sufficiently to permit removal of the tube.

Skin lesions. In 1929 Glaubersohn (30) described a triad of symptoms—ulcerations of the bowel, ulcers of the skin and hypochromic anemia. Brunsting, Goeckerman and O'Leary (31) reported an unusual type of ulceration of the skin occurring in adults with debilitating disease; four of their patients had chronic ulcerative colitis and one empyema. The condition was termed "pyoderma" denoting purulent infection of the skin. Similar cases have been reported recently by several authors (32, 37). Brooke (38) described a patient with chronic ulcerative colitis complicated by perirectal abscesses and erythema nodosum. He considered the two complications as related and suggested that erythema nodosum is simply an early stage of pyoderma gangrenosum, the severity and the chronicity of the underlying infection determining whether the erythema nodosum resolves or breaks down with ulceration. Felsen (39) relates three cases to avitamosis. Pyoderma gangrenosum was present in 0.3 per cent of his series. Bargen (4) noted an incidence of skin complications of 2.45 per cent.

In our series lesions of the skin were found in 41 of the 206. These have been classified as pyogenic, toxic, functional, and miscellaneous conditions not related to the ulcerative colitis.

Ten patients had pyogenic infections of the skin such as abscess formation, ecthyma, infectious eczematoid dermatitis, impetigo, decubitus ulcer, furuncle and pyoderma gangrenosum.

The most outstanding lesion is pyoderma gangrenosum, consisting of single or multiple necrotic ulcers sometimes quite large with bluish serpiginous borders and a moist base covered with mucopurulent exudate. The extent of the lesion can be so great as to almost denude a large area of the thoracic or abdominal wall. It may advance rapidly as the result of necrosis of the underlying subcutaneous tissue.

Four patients had erythemas of the toxic type but not related to drug ingestion; in four additional patients the toxic erythemas appeared to result from sulfonamide or phenobarbital therapy.

In the third group of so-called functional disorders of the skin, we have included eight patients with lesions such as dehydrosis, hyperhydrosis, necrotic excoriations, neurodermatitis, and static ulcer.

In the fourth group are 19 miscellaneous lesions of the skin certainly not related to the chronic ulcerative colitis.

Arthritis. Many patients have transitory painful swelling of the joints which disappears without residual deformity; in other the arthritis is more protracted and severe with definite roentgenologic evidence and persistent deformity. It is difficult to know whether these lesions are coincidental or related to the primary disease. In our series of 206 cases a diagnosis of arthritis was made in 16. Of these, eight were listed as having "arthritis," five of these of an acute type, four had rheumatoid arthritis and four a diagnosis of degenerative arthritis. Bargen (4) has reported an incidence of 4.33 per cent.

Venous thrombosis. Venous thrombosis is an infrequent complication. Bargen (40) described massive thrombosis of the extremities in a patient with chronic ulcerative colitis and carcinoma of the colon. Bargen and Barker (41) found in 1500 cases 18 with thrombophlebitis or arterial thrombosis so extensive as to become a grave clinical problem. Small thrombi in different organs such as the pelvic plexuses, lungs, spleen and kidney were present in 14 of 43 cases dying of ulcerative colitis. In three of these thrombosis was the immediate cause of death, gangrene of both legs being present in one. The incidence of massive thrombosis of the vessels was found to be slightly more than 0.1 per cent. Venous thrombosis occurred in four of our cases (1.94 per cent).

Hepatitis. As a rule patients dying with chronic ulcerative colitis are found at autopsy to have a marked fatty infiltration of the liver even though no evidence of hepatic dysfunction is detected during life. However, a careful study by means of the hepatic function tests may show a definite abnormality. Comfort, Bargen and Morlock reported five cases of chronic ulcerative colitis with slight or moderate jaundice, most of the with splenomegaly. The bromsulfalein tests showed a retention graded as III. In three the chronic hepatitis had apparently developed long after the ulcerative colitis appeared.

In a fourth case colitis and the jaudice appeared almost simultaneously. Other cases have been reported (42, 43).

It is very interesting that in non-specific ulcerative colitis in contrast to amebic colitis, hepatic and subdiaphragmatic abscesses and suppurative cholangitis occur very rarely. Landsbury and Bargen (43) in 1,333 cases found one with multiple hepatic abscesses (autopsy).

The impairment of the liver may be due to manifold causes such as the febrile course of the infection, the deficiencies in nutrition and perhaps also the administration of large doses of sulfonamides.

Septic complications distant from the colon. Not unusually patients with chronic ulcerative colitis have septic purulent foci distant from the colon. Characteristically the cultures from this pus show a rich and varied bacteria, both gram negative and gram positive organisms such as streptococci, staphylococci, b. coli, b. necrophorum, b. pyocyanus, etc. Surgical drainage is usually required. In 27 of the 206 cases septic infections occurred, an incidence of 13.10 per cent.

Peritonsillar abscess.....	1
Sinusitis.....	7
Parotitis.....	4
Epididymitis.....	4
Otitis media.....	3
Pyelonephritis.....	2
Pharyngitis.....	2
Osteomyelitis.....	1
Iridocyclitis.....	1
Laryngitis.....	1
Salpingoophoritis.....	1

One patient in an acute attack of the disease developed a left parotitis requiring surgical drainage; one month later a right parotitis likewise required surgical drainage. Parotitis probably results from the dryness of the mouth and the debilitated condition of the patient. The infections are practically staphlococcal or streptococcal and hence presumably could now be controlled by therapy with penicillin or sulfonamide or both.

4. *Complications Derived from Deficient Nutrition*

Malnutrition is common and is due primarily to the poor appetite and inadequate consumption of food. Other factors, however, may play a role such as continued fever, vomiting, diarrhea and defective intestinal absorption.

The mechanism of malnutrition and deficiency states in patients with diarrhea has been discussed by Bean and Spies (44). Mackie and Pound (45) found in chronic ulcerative colitis alterations in the lingual mucous membranes similar to those encountered in sprue, pellagra and pernicious anemia. They also noted in twenty-nine of the thirty-seven cases roentgenologic evidence of the small intestinal abnormalities observed in deficiency states: variation of

the contour and size of the lumen and alteration of the normal motor phenomena. The progress of the barium meal through the small intestine, however, was not abnormal (46, 47).

The deficient caloric intake of these patients is due primarily to poor appetite, the mechanism of which is not clear. The disease may directly or indirectly alter the motility of the small intestine and also of the stomach, thus affecting both appetite and hunger. Appetite is generally conceived to be central in origin related purely to the sight and smell of food, together with food memory and imagery whereas hunger is considered to arise from the contractions of the empty stomach. The validity of this distinction is open to question for various reasons not pertinent to this discussion. Regardless of the mechanisms involved, however, there can be no doubt of the fact that the sensations of appetite and hunger are both markedly impaired in certain acute disturbances of the digestive tract, such as food poisoning. Likewise chronic enteritis may be accompanied by a diminution in hunger and appetite. It is possible that there is not only a disturbance of the motility of the intestinal tract but also an impairment of digestion and of absorption. Zetzel (48) et al. found in five cases of chronic ulcerative colitis a marked impairment of absorption of an enzymatic hydrosilicate of casein. Generalized osteoporosis, with low levels of serum calcium may occur as seen in one of our cases. Bargen (4) reported an incidence of tetany of 1.0 per cent in patients of chronic ulcerative colitis. Mackie (49) found evidence of avitaminosis in 62 per cent. Crohn (50) described cases with xerophthalmia. Lerner and Davenport (51) found objective evidence of subclinical avitaminosis in 41 per cent of a group of 30 patients, twice the normal expectancy. On the other hand, it is surprising how infrequently one sees frank evidence of avitaminosis. Pellagra has been reported (37) and Kindschi (52) describes an unusual case with clinical pellagra and beriberi both of which responded well to vitamin therapy. Page and Bercowitz (20) found definite evidence of Vitamin K deficiency as evidenced by hypoprothrombinemia in 28.8 per cent of the patients with chronic ulcerative colitis. The same authors (53) found abnormal reactions to oral dextrose tolerance tests; none of the intravenous dextrose tests were normal, although the metabolism of dextrose as determined by basal metabolic rates and respiratory quotients was normal. A relatively small per cent of the patients had low fasting plasma Vitamin A carotene and Vitamin C levels. Peripheral neuritis was observed in 3 cases, an incidence of 4 per cent.

As a result of a deficient nutrition in children with long standing chronic ulcerative colitis mild and severe forms of genital hypoplasia occur together with delayed appearance of the secondary sexual characteristics and somatic hypoplasia. In young girls amenorrhea is observed. Infantilism was first reported in such patients by Davidson (54) in 1939. Benson and Bargen (55) studied the mild and severe forms of infantilism in 14 cases; many others have

been reported (17, 56, 57). In 23 children in this series three cases with definite infantilism were noted, an incidence of 13.1 per cent.

5. *Miscellaneous Complications*

Other complications have been reported, some of them very unusual such as esophageal ulcer (58). Lindhal and Bargen (59) considered nephrolithiasis to be more frequent among patients undergoing surgery. Paviot et al. (60) reported an instance of paraplegia attributed to myelitis. Bargen et al. (61) described intussusception. Peters (62) reported pigmentation of the skin suggesting adrenal insufficiency and responding fairly well to cortical therapy. Welch et al. (63) described psychosis, schizophrenic catatonic in type, disappearing after a two-stage resection of the diseased colon. Splenomegaly was found by Bargen (4) in one per cent of his cases. Involvement of the pleura has been described, effusion being present in two of our patients without apparent tuberculosis. Endocarditis (4) was described by Bargen in one per cent, an incidence of 0.97 per cent. In two of our cases there was evidence of endocarditis. Schlike and Bargen (64) observed five men and two women with "clubbed" fingers.

Associated diseases. Many conditions apparently unrelated to the primary disease have been noted:

Pulmonary tuberculosis (apparently arrested in 3).....	5
Obesity.....	3
Pilonidal cyst.....	2
Osteoarthritis.....	4
Rheumatic heart disease.....	2
Cholelithiasis.....	3
Epilepsy.....	2
Cancer.....	3
Allergic rhinitis.....	2
Arteritis.....	1
Brachilia neuritis.....	1
Varicose veins.....	1
Nerve deafness.....	1
Lues.....	1
Schizophrenia.....	2
Hernia.....	2
Endometriosis.....	1
Renal calculus.....	1
Gastric carcinoma.....	1
Hypernephroma.....	1
Amebiasis.....	7
Goiter.....	1
Onychomycosis.....	1
Diabetes mellitus.....	1
Hypertension.....	1
Optic nerve atrophy.....	1
Cirrhosis of the liver.....	1
Diverticulosis.....	1

Question might properly be raised as to the relationship between amebic colitis and non-specific ulcerative colitis. The patients so included in this paper were ones in whose feces *E. Histolytica* were demonstrated in this clinic or alleged to have been found elsewhere and in whom disease persisted after eradication of the ameba. In all the proctoscopic appearance was that of a uniformly and diffusely friable, granular mucosa typical of non-specific ulcerative colitis in contrast with the classical discrete circumscribed ulcers of amebic colitis.

SUMMARY AND CONCLUSIONS

1. In a series of 206 cases of chronic non-specific ulcerative colitis complications were present in 64 (31.06 per cent).
2. The complications have been classified into five groups: (1) those involving the colon itself, (2) those involving adjacent structures, (3) those distant from the colon, (4) complications resulting from deficient nutrition and (5) a miscellaneous group.
3. The complications in the first group may be tested as follows: polyps 21 (10.00 per cent), stricture 8 (3.9 per cent), obstruction 6 (2.9 per cent), and carcinoma 3 (1.4 per cent). Hemorrhage occurred quite frequently but there was no fatality from this cause. Ulcerated hemorrhoids were noted in 13 cases (6.8 per cent). In the second group internal or external fistulae were found in 9 cases (4.4 per cent). Perforation with peritonitis was observed in 7 cases (3.4 per cent). Complications distant from the colon were as follows: lesion of skin and mucosal surface 22 (10.64 per cent), arthritis 12 (5.82 per cent), venous thrombosis 4 (1.94 per cent), hepatitis 1 (0.48 per cent) and septic infection 27 (13.10 per cent). Among the complications derived from deficient nutrition were listed malnutrition and avitaminosis although the incidence and severity of these could not be determined. In a sub-group of 23 children there were 3 cases of infantilism, an incidence of 13.1 per cent. Peripheral neuritis was observed in 3 cases (1.45 per cent). A miscellaneous group of complications included several conditions such as pleuritis, 2 cases (0.97 per cent) and endocarditis 2 cases (0.94 per cent).
4. Many conditions unrelated to the primary disease are listed.
5. The significance of the various complications has been discussed.

REFERENCES

1. JACKMAN, RAYMOND J., BARGEN, J. ARNOLD, AND HELMHOLZ, HENRY F.: Am. J. Dis. Child., 59: 459, 1940.
2. SCHLICKE, CARL P., AND BARGEN, J. ARNOLD: Minnesota Med., 23: 348, 1940.
3. VIRCHOW. Quoted by Bargent and Comfort.
4. BARGEN, J. ARNOLD: Annals of Int. Med., 3: 335, 1929.
5. BARGEN, J. ARNOLD, AND COMFORT, MANDRED W.: Ann. Int. Med., 4: 122, 1930.

6. FELSEN, JOSEPH: *Bacillary Dysentery, Colitis, Enteritis.* W. B. Saunders Co., 1945.
7. STREICHER, M. H.: *Am. J. Dig. Dis.*, 5: 361, 1918.
8. LUND, F. B.: *New Eng. Jr. of Med.*, 206: 156, 1932.
9. EWING, JAMES: *Neoplastic Diseases.* W. B. Saunders Co., 1942.
10. BARGEN, J. ARNOLD: *Southern Med. Jr.*, 32: 627, 1939.
11. BARGEN, J. ARNOLD: *Arch. Surg.*, 17: 561, 1928.
12. BARGEN, J. ARNOLD, AND DIXON, CLAUDE, F.: *Arch. Surg.*, 30: 854, 1935.
13. BARGEN, J. ARNOLD, AND SAUER, WILLIAM G.: *Clinics*, 3: 516, 1944-45.
14. GAUSHORN, J. A.: *Chronic Ulcerative Colitis and Carcinoma: a Pathological Study.* Thesis Graduate School, Univ. of Minn., 1938.
15. MATZNER, MILTON J., AND SHAEFER, GEORGE: *Review Gastroenterol.*, 6: 422, 1939.
16. BOROS, EDWIN: *Med. Jr. and Record.*, 135: 383, 1932.
17. RICKETTS, WILLIAM E., BENDITT, EARL, AND PALMER, WALTER L.: *Gastroenterology*, 5: 272, 1945.
18. SEALY, W. B., AND BROWN, P. W.: *Proc. Staff Meet. Mayo Clin.*, 15: 498, 1940.
19. RAMOS, MYRA MANUEL: *Arch. Arg. de Enf. del Ap. Dig. y de la Nut.*, 19: 273, 1944.
20. PAGE, ALBERT C., AND BERCOVITZ, Z.: *Amer. Jr. Dig. Dis.*, 9: 419, 1942.
21. BARGEN, J. ARNOLD, KER, J. G., HAUSNER, ERICH AND WEBER, H. M.: *Proc. Staff. Meet. Mayo Clin.*, 12: 385, 1937.
22. ORMANDI, L., AND BARGEN, J. ARNOLD: *Proc. Soc. Staff. Meet. Mayo Clin.*, 14: 550, 1939.
23. BARNES, JOHN M.: *Annals of Clin. Med.*, 4: 552, 1925.
24. BOCKUS, HENRY L.: *Gastroenterology*, 2: 592, 1944, W. B. Saunders Co., 1944.
25. CRANDON, JOHN, KINNEY, THOMAS, D., AND WALKER, IRVING: *New Eng. Jr. of Med.*, 230: 419, 1944.
26. BARGEN, J. ARNOLD, AND JACOBS, MINIARD F.: *Arch. Int. Med.*, 43: 483, 1929.
28. PALMER, WALTER L., AND RICKETTS, WILLIAM E.: *Arch. Surg.*, 51: 102, 1945.
29. UNGAR, J.: *Nature*, 162: 245, 1943.
30. GLAUBERSON, S. A.: *Dermat.*, 88: 497, 1929.
31. BRUNSTING, LOUIS A., GOECKERMAN, WILLIAM H., AND O'LEARY, PAUL A.: *Arch. Dermatol.*, 22: 655, 1930.
32. LANE, CLINTON W., AND STROUD, C. MALONE: *Arch. Dermatol. and Syph.*, 27: 460, 1933.
33. COHEN, MILTON H.: *Arch. Dermatol. and Syph.*, 33: 813, 1936.
34. JANKELSON, I. R., AND MASSELL, B. F.: *Amer. Jr. Dig. Dis.*, 3: 19, 1936.
35. JANKELSON, I. R., AND MCCLURE, CHARLES W.: *Acta Dermato venerologica.*, 41: 255, 1940.
36. MINTZER, IDA J.: *Arch. Dermatol. and Syph.*, 40: 541, 1939.
37. COWETT, MAX P.: *Amer. Jr. Surg.*, 38: 364, 1937.
38. BROOKE, P. A.: *New Eng. Jr. of Med.*, 209: 233, 1933.
39. FELSEN, JOSEPH: *New York State Jr. of Med.*, 41: 2228, 1941.
40. BARGEN, J. ARNOLD, AND COFFEY, ROBERT J.: *Med. Clin. of North Amer.*, 19: 403, 1935.
41. BARGEN, J. ARNOLD, AND BARKER, W.: *Arch. Int. Med.*, 58: 18, 1936.
42. MCCANNEL, D. A.: *Proc. Soc. Staff. Meet. Mayo Clin.*, 14: 38, 1939.
43. LANDSBURY, JOHN, AND BARGEN, J. ARNOLD: *Med. Clin. North Amer.*, 16: 1427, 1933.
44. BEAN, W. B., AND SPIES, T. D.: *J. A. M. A.*, 115: 1078, 1940.
45. MACKIE, THOMAS T., AND POUND, ROBERT E.: *J. A. M. A.*, 104: 615, 1935.
46. LEPORE, MICHAEL J., AND GOLDEN, ROSS A.: *J. A. M. A.*, 117: 918, 1941.
47. GOLDEN, ROSS: *Radiol.*, 36: 262, 1941.
48. ZETZEL, L., BANKS, B. M., AND SAGALL, E.: *Amer. Jr. Dig. Dis.*, 9: 350, 1942.
49. MACKIE, T. T.: *Am. Proct. Soc.*, 35: 97, 1934.
50. CROHN, BURNELL B.: *Amer. Jr. Med. Sci.*, 169: 260, 1925.
51. LERNER, HENRY H., AND RAVENPORT, HOWARD G.: *Amer. Jr. Dig. Dis.*, 6: 239, 1939.
52. KINDSCHI, L. G.: *Proc. Soc. Staff. Meet. Mayo Clin.*, 14: 686, 1939.
53. BERCOVITZ, Z., AND PAGE, R. C.: *Ann. Int. Med.*, 20: 239, 1944.
54. DAVIDSON, SIDNEY: *Arch. Int. Med.*, 64: 1187, 1939.

55. BENSON, RAYMOND E., AND BARGEN, J. ARNOLD: Gastroenterol., **1**: 147, 1943.
56. ESPEJO-SOLÁ JAIME, SOLÁ OSCAR H., AND RATELL, GUILLERMO: El Dia Medico, **16**: 770, 1944.
57. KINDSCHI, L. G.: Proc. Soc. Staff Meet. Mayo Clin., **14**: 686, 1939.
58. CABOT, RICHARD: Case #15081. New Eng. Jr. of Med., **200**: 392, 1929.
59. LINDAHL, WALLACE W., AND BARGEN, J. ARNOLD: Jr. of Urol., **46**: 183, 1941.
60. PAVIOT, M. M. J., GUICHARD, A., AND PLANCHU, M.: J. de Med. de Lyon, **18**: 33, 1937.
61. BARGEN, J. ARNOLD, KER, J. G., HAUSNER, ERICH, AND WEBER, H. M.: Proc. Staff Meet. Mayo Clinic, **12**: 385, 1937.
62. PETERS, G. A.: Proc. Staff Meet. Mayo Clin., **19**: 303, 1944.
63. WELCH, C. STUART, AND GORHAM, L. WHITTINGTON: Amer. J. Surg., **52**: 511, 1941.
64. SCHLIKE, CARL P., AND BARGEN, J. ARNOLD: Amer. J. Dig. Dis., **7**: 17, 1940.

THE ETIOLOGY OF ULCERATIVE COLITIS: AN ANALYTICAL REVIEW OF THE LITERATURE

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INTRODUCTION

The literature pertaining to the etiology of ulcerative colitis has been reviewed by us for three reasons. First, the subject has not been analytically reviewed recently; second, we plan to undertake some studies on the problem; and, third, a review may serve to stimulate others to investigate the problem experimentally.

Emphasis will be placed on the experimental rather than the clinical aspects of the problem. The latter will be reviewed only to develop the different viewpoints, which, however, are in most instances parallel with the various experimental approaches to the problem. For example, experimental work has been done on the infectious, allergic, mechanical and vascular theories of the etiology of the disease which are directly related to some of the etiological theories suggested by clinical considerations.

We shall first review the experimental observations and then refer to the clinical observations and evidence more briefly, since the latter are probably better known.

EXPERIMENTAL PRODUCTION OF ULCERS OF THE COLON

Infectious Agents

Diplococcus or diplostreptococcus. In 1924, Bargen (1) submitted experimental evidence indicating that a diplococcus might be the cause of the production of "thromboulcerative colitis". Cultures were made from the cleansed base of the ulcers of 22 patients. Two organisms predominated, a diplococcus and a gram-negative bacillus, probably the colon bacillus. The former grew in predominance in the dextrose-brain broth he used. One hundred and ninety rabbits were injected intravenously and 56 developed lesions in the colon ranging from disseminated petechial hemorrhages and massive hemorrhages to superficial ulcers of the mucosa "from the rectum upwards". Eleven of the 56 had received pure cultures of diplococci and 45 had received mixed cultures; 65 had no diarrhea or lesions, only 2 animals had extra-intestinal lesions. "A few rabbits were given the gram-negative bacilli alone in dextrose-brain broth; they died within 24 hours without lesions of the colon." Cultures made from the cleansed mucosa of 4 patients without ulcerative colitis, were each injected into 2 or 3 rabbits; only one animal developed petechial hemorrhages of the colon and the particular culture used contained diplococci.

Bargen and Logan (2) in 1925 reported more extensive experimental results. Diplococci were cultured from the ulcers of 80 per cent of 68 patients, diplococci being found in cultures of the cleansed mucosa in only 1 of 20 persons without ulcerative colitis. In this report 139 rabbits were injected with 5 to 15 cc. of the broth containing diplococci and lesions of the colon occurred in 45, gross lesions being absent from other organs. They refer to Rosenow as not having seen lesions of the colon when various streptococci were injected into rabbits like those caused by the diplococcus. Nine rabbits kept on a vitamin-deficient diet for two weeks were injected with 5 cc. of the diplococcus containing broth and all died within 5 days. Eight had lesions of the colon, three of which had empyema of the gallbladder in addition. Two young dogs were daily injected intravenously with the diplococcus from the gall bladder of the rabbits. They both developed bloody stools and ulcerative colitis, as detected by proctoscopy; however, the dogs apparently developed an "immunity", since one showed recovery at 2 weeks and the other at 3 weeks, though the injections were continued. Diplococci and streptococci isolated from a periapical abscess of a patient with ulcerative colitis were cultured, as usual, and injected intravenously into a rabbit which died of colonic lesions. A subculture of the mesenteric glands was made and injected into 2 dogs which died with extensive lesions of the colon and intestine, no lesions being found elsewhere. A pure culture of a diplococcus was obtained from the pus of miliary abscesses which developed in the protruding mucosa of an ileostomy stoma of a patient with ulcerative colitis. These diplococci were not injected into animals. These authors did not inject the broth or autoclave broth cultures to control their effect.

Butiaux and Sevin (3) isolated a diplococcus from a patient with ulcerative colitis and found that it had a particular affinity for the colon of rabbits. The number of rabbits studied was not stated; but they cite a protocol of a rabbit which survived the acute attack and developed a stricture of the colon. Another rabbit in addition to lesions of the colon developed arthritis and myositis.

Cook (4) in 1931 performed a well designed series of experiments, the results of which strongly support the experimental results of Bargen and Bargen and Logan. He cultivated a diplostreptococcus from the abscessed teeth of patients with active ulcerative colitis. Sixty rabbits were injected intravenously with the usual broth culture and 60 per cent of them developed diffuse hemorrhagic infiltrations of the colon; 21 per cent of the rabbits had lesions elsewhere, chiefly in the muscle (8 per cent). Heat inactivated broth controls were not used. He inoculated the teeth of 15 dogs with a diplococcus isolated from the teeth of patients with ulcerative colitis. Seven developed diarrhea and ulcers of the colon, which were detected and followed proctoscopically,

from 8 to 16 months after the inoculation. An illustrative protocol of one of these dogs is given. This dog was inoculated November 14, 1926 and developed definite colitis in July, 1927, which had abated by December, 1927. In February, 1928, the animal was experimentally chilled and developed a recurrence of ulcerative colitis which persisted acutely for 4 weeks when the animal was etherized. The diplococcus from the teeth of dogs inoculated months previously was cultured and injected, as the broth, into 60 rabbits, 45 per cent of which developed acute colitis, other organs being involved in 25 per cent of the rabbits. Sixty rabbits were also injected with the broth culture of the teeth of the dogs at the end of the experiment; 40 per cent developed colitis and 21 per cent had lesions of other organs.

Cook controlled his studies in two ways. He cultured (dextrose brain broth) the pulpless teeth of 15 patients with disease other than colitis. Sixty rabbits were injected and only 1 developed colitis. He also inoculated the teeth of 15 dogs, killing one usually after the death of one of the dogs inoculated with diplococci from the teeth of patients with ulcerative colitis. These animals all remained normal and the organs were normal at autopsy. However, cultures of the teeth of these control dogs were made and injected into 60 rabbits, "none developed colitis, but the elective localizing power for other tissues had been retained apparently to some extent". In Cook's article it is clear that in some cases a "pure" culture of diplostreptococci was used; in other cases it is not clear.

Paulson (5) isolated seven types of streptococci from the ulcers of patients with ulcerative colitis, using dextrose-brain broth. He injected 34 rabbits intravenously, 14 of the 30 examined had intestinal lesions and 12 had hemorrhage into or ulcers of the cecum, colon, rectum or anus. Among the 6 of the 34 rabbits which received "Bargen's diplococcus" only, 1 had a colitis. The lesions produced were located primarily in the colon and rectum. Extra-enteric lesions were present in 4 of the 30 rabbits but in 2 of these the chief pathology was intestinal; there were no lesions of the stomach. Seven types of streptococcus were then isolated from other sources than the ulcers of patients with ulcerative colitis. The organisms were *B. dysenteriae* (Shiga and Flexner), *B. coli*, and streptococci (alpha and beta zoned colonies) from the throat (2 cases) and the uterus (1 case). Ten of the 16 rabbits which died or were killed showed lesions of the cecum, colon, or rectum, and only one of the 16 had an extra intestinal gross lesion. Of these 10, 3 of the lesions of the colon were caused by *B. dysenteriae* which is known to cause lesions of the colon frequently when injected parenterally. Of the remaining 7 cases of colon lesions, *B. coli* was used in 3 and streptococci in 4 cases. Paulson, like the two preceding investigators, did not inject sterilized broth.

In 1933, Buie and Bargen (6) summarized the experimental observations

made during a period of 10 years. Cultures had been made from the nose and throat of 543 patients without ulcerative colitis, and injected into rabbits. Lesions were found in the colon in only 0.8 per cent of the rabbits. This should constitute a good control for the effect of the broth alone. From 1100 patients with chronic ulcerative colitis 815 strains of diplostreptococci were isolated; 500 of these were injected into 1,000 rabbits, 65 per cent of which developed acute lesions of the colon. Diplostreptococci were isolated from apical dental abscesses in 148 patients with chronic ulcerative colitis and injected into rabbits, 75 per cent of which developed colonic lesions. Similar results were obtained with diplococci isolated from the tonsils of 100 patients with chronic ulcerative colitis. Swabbings from 100 normal colons when cultured showed diplococci in only 4 cases. *B. dysenteriae* was not obtained when specimens removed from 56 patients with ulcerative colitis were cultured.

Paulson (7) reviewed the literature in 1933 and included a critique of the observations of Bargen and his colleagues. In this article he points out that streptococci or organisms from foci of other types of hemorrhagic or ulcerative colitides were not used by Bargen and his colleagues. We agree that it would be well to know if diplococci could be cultured from the ulcers of the colon due to tuberculosis, ameba, or the dysentery bacillus. He points out that when Cook infected the teeth of his dogs he used "primary cultures which may or may not have been pure." We agree that it would have been advisable for Cook to have been more clear regarding the flora of his primary cultures; however, Cook in his control series also used primary cultures from non-ulcerative colitis patients and obtained no colitis in the 15 dogs used. Paulson points out that the characteristics of the diplostreptococci studied in Bargen's reports varied, which questions the specificity or the constancy of the organism claimed to produce the lesion. This is true provided one assumes that a specific organism must not manifest strains and adaptations. There are types of pneumococci all of which cause lesions of the lungs; there are types of dysentery bacilli all of which cause intestinal lesions when given parenterally to rabbits. Even *B. necrophorum* growing in an ulcer of the colon of a patient causes the development of agglutinins in the patient which are more specific for the patients' *B. necrophorum* than for the *B. necrophorum* of another patient according to Dragstedt, Dack and Kirsner (36). Paulson further argues that the predominance of diplococci in Rosenow's dextrose-brain broth is of no significance because "it is a selective medium." This is not a significant argument, in our opinion, because everyone uses selective media in isolating and culturing organisms. However, in using selective media, it is always shown that other organisms which are and are not selected by the media do not cause the lesion being studied. Thus, in our opinion, the only observation made by Paulson which is contrary to the observations of Bargen and his group, is that strepto-

cocci which do not conform to the cultural and morphological characteristics of Bargen's diplostreptococcus may be selected by dextrose-brain broth and cause acute lesions of the colon of rabbits; also, that *B. coli*, presumably in pure culture, caused lesions of the cecum of 3 of 4 rabbits injected. If *B. coli* does produce lesions of the colon when given parentally, such is not proof that diplococci and other organisms located in a focus of infection may not be responsible for causing acute lesions of the colon and starting them on the road to chronicity.

Lups (144) produced colitis in several of 15 rabbits on injecting diplococci isolated for patients with ulcerative colitis.

Mones and Sanjuan (8) injected various bacteria into rabbits and dogs and found that characteristic lesions of the colon occurred rarely. They isolated several organisms (*S. fecalis*, *mitis*, *saprophyticus*, etc.) from 21 patients with ulcerative colitis and injected the culture into an unstated number of rabbits. Using Rosenow's medium they obtained lesions solely in the intestines in 3 instances and of many organs in 3 instances. Similar organisms were isolated from 25 patients with disease other than colitis. Using Rosenow's medium, they observed lesions only of the intestine when the organism from 1 patient was injected, and of many organs when the organisms of 5 patients were injected. Among the 25 patients with ulcerative colitis, they isolated diplo-streptococcus in all but classified them as *S. fecalis*, *mitis*, *saprophyticus*, etc. Among 25 patients who did not have colitis, they cultured essentially the same organisms. They were more impressed by the results of animal experiments which were designed to detect the presence of a virus as the etiological factor. They interpreted their results as indicating that *a virus* is involved in the etiology of chronic ulcerative colitis, but its action is difficult to separate from the action of bacteria which play an important but secondary part.

Comment. The results of the authors from the Mayo Clinic and the Pasteur Institute show clearly that the injection of Bargen's diplococcus or other organisms in dextrose-brain broth may produce *acute* ulcerative colitis in rabbits and dogs. None of the authors injected the broth alone or autoclaved cultures to determine to what extent the broth alone might produce lesions of the colon and other organs of rabbits and dogs. The failure to obtain lesions of the colon in a large per cent of animals may legitimately be considered an adequate control. However, the results observed by Cook, when he injected cultures derived from the pulpless teeth of patients with disease other than ulcerative colitis into 60 rabbits and observed only 1 to develop colitis, is strongly presumptive evidence that the broth is not involved in the cause of the ulcers and that the streptococcus from cases of ulcerative colitis is definitely "elective" in character. Even Paulson's streptococci, isolated from patients without colitis, were apparently quite "elective" for the colon, since 9 animals

were injected and 4 developed lesions of the colon, 4 had no lesions, and 1 had lesions only of the small intestine. This raises the question: Might not the broth cause injury of the blood vessels of the colon directly or by causing a contraction of the colonic musculature which provides areas of lowered resistance for streptococci? One wonders what might occur if lesions of the mucosa were produced by an injection of pilocarpine and then the organisms in normal saline (i.e., not in the broth) injected. The possibility that some or several factors operate to lower the susceptibility of the colon to streptococci, a suggestion made by many authors, deserves serious experimental consideration.

Paulson's observations on the non-specificity of Bargen's diplococcus for the colon of rabbits are definitely opposed to those of Bargen, of Bargen and Logan, and of Cook. They are also opposed to the *remarkable* observations of Cook when he innoculated the teeth of one group of dogs with "diplococci" from patients with ulcerative colitis and a control group with streptococci from patients not having ulcerative colitis. The one protocol he presents, if it is true of the remaining 6 dogs, simulates in a remarkable way the course of recurrent ulcerative colitis in man. The results on rabbits only show that acute lesions of the colon may be produced by streptococci. Cook's work on dogs shows not only a striking specificity of the "diplostreptococci" he used but reproduces the disease of man as well as one might reasonably expect it to be produced. The experiment of Cook certainly should be repeated in view of the existing doubt regarding the theory of the tissue specificity of streptococci and the streptococcic origin of a major portion of the cases of chronic ulcerative colitis.

Paulson's observations that lesions of the colon may be produced by the injection of *B. coli* and various streptococci cultured in dextrose-brain broth should be repeated. It would be important to know which bacteria other than the dysentery and typhoid group will produce lesions in the gastrointestinal tract when given parenterally to laboratory animals.

The major experimental etiological problem is not to prove that an organism is specifically concerned in the genesis and maintenance of chronic ulcerative colitis. *The major etiological experimental problem is to ascertain whether chronic ulcerative colitis is infectious in regard to onset and chronicity*, which means that attempts should be made to reproduce on an infectious basis the condition as it occurs in man. Buttiaux and Sevin, and particularly Cook, have provided the only unchallenged evidence of this type.

B. dysenteriae. Rabbits. Many investigators have reported lesions of the small intestine, cecum and colon of rabbits when Shiga toxin is injected intravenously; given orally or into the intestine it has no effect. Only a few references will be cited (9-16). Gardner (9) states that when the dose of

Shiga toxin in rabbits is not too large a thickening of the intestinal wall with ulcerative changes in the cecum and large intestine occurs. This yields a picture simulating human dysentery, though Kruse (10) has expressed the opinion that the human type of dysentery has not been produced in animals.

It is very difficult to give rabbits dysentery by giving the dysentery bacilli orally or directly into the intestine (9-13); successful cases are rare (18-19). Rabbits, when injected parenterally with the organism, develop lesions in the intestine, cecum and colon (9, 11, 13, 17). (The same is true of young pigs (11) which have a colon anatomically like that of man.)

Cats. Shiga (20) gave a cat a drop of croton oil and then some Shiga bacilli orally. The animal developed the clinical and bacteriological evidence of dysentery and died 4 weeks later, the mucosa being covered with mucus from which the organism was isolated.

Dogs. Dold and Fischer (21) and Dold (22) have described a natural dysentery (Shiga) in dogs with ulcers of the colon. Gardner (9) states that dogs may occasionally contract the Flexner type of dysentery naturally, and that the dog is susceptible to artificial infection. Vaillard and Dopter (11) obtained lesions of the intestines and colon in dogs by the parenteral injection of Shiga bacilli. Reid, Anderson, Stubblefield and Ivy (17) studied the effect of the intravenous administration of Shiga toxin in a large number of dogs. Petechial hemorrhages in the stomach, hemorrhagic pseudomembranous enteritis, and hemorrhages into and ulceration of the colon were found. Lium (23) produced ulcers in exteriorized patches of the dog's colon by injecting non-fatal doses of Shiga toxin. The punctate ulcers produced healed in 4 to 9 days. Lesions were produced three times in one dog by injecting the toxin at 3 to 5 day intervals.

Monkeys. Naturally occurring bacillary dysentery (Shiga and Flexner) has been described in monkeys in captivity (24-28). Flexner (29) was unable to produce the disease by feeding the Flexner organism to monkeys. However, Dack and Petran (30) were successful in producing the disease (Flexner) in two rhesus monkeys by feeding a culture. One died on the second day with hemorrhages and ulcers of the colon. They also produced the colitis by inoculating a loop of the colon isolated as a Thiry-Vella fistula. Forty-eight hours after the inoculation the animals became ill and a bloody discharge passed from the loop for from 4 to 5 days, after which the animals recovered. Both of these monkeys developed agglutinin titers, but the colon *in situ*, through which the fecal stream passed, did not become infected.

Comment. None of these observers followed the animals which recovered from the acute effects of an inoculation or an injection of toxin to ascertain the after effects on the colon. The statement of Gardner (9) to the effect that a sublethal dose of toxin caused a picture simulating human dysentery is inter-

esting and should provoke further work with repeated doses of dysentery toxin. In those reports dealing with the immunization of animals by repeated doses of toxin, we have found no observations regarding the condition of the colon (9). This would be significant, since the effect of Shiga toxin on the colon is the same as that of the bacillus. There is no evidence from the experimental work on dysentery that a condition simulating chronic ulcerative colitis has been produced.

B. necrophorum. Dragstedt, Dack, and their colleagues (29—33) have suggested that *B. necrophorum* (or *funduliformis*) seems capable of continuing and extending an ulcer of the colon after some additional factor produces the primary lesion. The circumstantial evidence on which they base their suggestion may be outlined as follows. The organism was found in the colon of 70 per cent of 298 patients with chronic ulcerative colitis. The culture of swabbings of the ulcerated areas usually yielded the organism, whereas the organism was not found in the swabbings of 99 patients with a normal colon. The organism has been found repeatedly in the isolated colon of 12 patients with an ileostomy performed for ulcerative colitis. Complement-fixing antibodies and agglutinins for the organism have been found in the serum of patients with ulcerative colitis, and the titer of agglutinins is higher for the patient's strain of the organism than for that of another patient.

They have not been able to produce ulcers of the colon by feeding the organism by mouth, by rectal instillation, and by introducing it into the isolated colon of dogs, monkeys and baboons. The same is true of the bloody, purulent discharge of patients with the disease; this is similar to the inability, except in rare cases, to produce dysentery in animals by oral or intestinal administration.

Rabbits do not develop an immunity to the organism on repeated subcutaneous injection, a fact which favors chronicity.

Meleny (37) was able to find *B. necrophorum* in only 3 of 40 cases of chronic ulcerative colitis, though the organism is very sensitive to oxygen and may be overgrown by other bacteria common to the colon.

Fry and Dack (33) introduced the organism into the isolated colon of a dog and was able to recover them after 12 hours in "appreciable numbers". When the colon was aerated with oxygen for 90 minutes no organisms were recovered. This may bear some relation to the Felsen's (38) observation regarding the apparent benefit of administering oxygen per rectum to patients with ulcerative colitis.

Comment. It would be of interest to ascertain whether *B. necrophorum* experimentally injected into necrotic areas of the colonic mucosa in the animals would cause chronicity and extension.

Meleney has remarked that the persistence of the organism in the isolated colon of the patient is significant as is the presence of a high agglutinin titer of the patient's serum for the strain which inhabits the patient's colon. He also

reports 3 patients in whom zinc peroxide, administered by irrigation or given as retention enemata, restored the patient's colon to a normal contour.

Virus. Mones and Sanjuan (8) made scrapings of intestinal mucosa and suspended them in a saline solution. The filtrate was injected intravenously and into the brain of rabbits and lesions in the bowel resulted. These authors expressed the view that a filterable virus is the cause of the lesions of ulcerative colitis.

Paulson (39, 40), on the supposition that a virus might be concerned, prepared an antigen from the colonic exudate of patients with chronic ulcerative colitis with and without a Frei reaction. He obtained positive cutaneous tests in 6 patients with ulcerative colitis and positive Frei tests, and negative tests in 12 of 13 control cases with and without colitis and with negative Frei test. Rodaniche, Kirsner, and Palmer (41) obtained positive tests in 2 and negative tests in 31 patients with ulcerative colitis. They conclude that lymphogranuloma venereum and non-specific colitis are unrelated but in their early stages resemble each other clinically and proctoscopically.

ALLERGIC ULCERS OF THE COLON

The studies of Gray and Walzer (42) on mucous membrane hypersensitivity in passively sensitized animals are significant contributions. In both animals and humans (43, 44) they injected human serum containing reagin antibodies for peanut locally into the bowel. One to two days later a peanut meal fed by mouth caused the site of local injection to become rapidly edematous and hyperemic. When this was done close to the rectal mucosa (in humans) the patients had an immediate desire to evacuate with a sense of fullness, pruritis, and marked irritation. A somewhat similar observation was made by Atkinson (45). He produced lesions in the exteriorized segment of the colon of a dog by injecting locally a variety of foreign proteins and later injecting the same proteins intravenously. However, as in the case of acute ulcers produced in the stomach by Shapiro and Ivy (46), on the basis of a local allergic reaction these ulcers of the colon could not be maintained in a chronic condition, because the animals became immune.

So, if an allergic reaction is the cause of chronic ulcers of the colon, the patient's allergy must be of the type that is not readily subject to desensitization, and the only recourse is to withdraw the allergin.

MECHANICAL TRAUMA

It is well known that the injection of foreign protein into an animal frequently causes vomiting, defecation and tenesmus followed by quiescence (47). The injection of Shiga toxin in from 30 to 40 minutes usually caused defecation, diarrhea, and tenesmus, followed by the frequent passage of blood stools (17, 48).

Lium (23) has made an interesting study of the effect of various substances on the mucosa of colonic explants in the dog. He found that small traumatic ulcers healed in 4 days and that the regenerated epithelium was quite sensitive to trauma. Marked contraction of the explant, caused by acetyl choline and prostigmine caused bleeding and hemorrhagic erosions of the mucosa. Shiga dysentery toxin caused first a spasm of the musculature, the secretion of thick and then thin mucus, edema, petechial hemorrhages, bleeding and punctate ulcers which bled easily. The mucosa of the patch returned to normal within 4 to 9 days. The lesions of the mucosa were produced 3 times in one dog at 3 to 5 day intervals. When the toxin was placed on the mucosa no change occurred. He observed that blanching of the mucosa without contractions of the muscularis caused no lesions of the mucosa.

Lium argues that since spasm is so important in causing acute lesions, ulcers of the colon should be found chiefly in the rectum, and that is where the lesions in 95 per cent of cases of ulcerative colitis start. When they occur higher up in the colon they should occur chiefly in the vicinity of the tenia, which is the case according to Virchow's and Lium's observations (140).

VASCULAR CHANGES

Congestion of the mucosa and increased motility of the gastrointestinal tract occur at least for a time in non-fatal anaphylactic shock. In some instances petechial hemorrhages into the mucosa also occur.

Penner and Bernheim (49) produced experimental shock in 6 dogs, 6 cats, 6 rabbits, and 4 guinea pigs by intraperitoneal injection of adrenalin. They found gross changes in the ileum, colon, and gastric mucosa consisting of large ulcerations and pseudo-diphtheritic membrane formation. These authors suggest that vasospasm, if of sufficient severity and duration, is a factor to be considered in ulceration of the gastro-intestinal tract. Ecker and Biskind (50) under direct observation of the rabbit's intestine during anaphylactic shock found that the intestine showed irregular spastic contractions and marked peristaltic rushes in the cecum and lower colon. The factor of vasospasm undoubtedly plays a secondary role in the etiology of ulcerative colitis.

These observations simply indicate that mechanical disturbances of the vascular supply of the mucosa, as found by Lium, can produce acute lesions. In addition, in an allergic reaction the permeability of the capillary wall is increased, probably associated with a local arteriolar spasm due to the release of histamine. We have found no work based upon the hypothesis that ulcers may be produced or be due to thrombosis or emboli, a theory which held such an important place in the etiology of peptic ulcer for more than half a century, and one that is still referred to frequently.

OBSTRUCTION OF LYMPHATIC SUPPLY

Poppe (51) obstructed the lymphatic supply of the proximal colon of 15 dogs by injecting sclerosing substances. Acute ulceration of the mucosa of the colon occurred in 5 of the animals. He injected *B. coli*, *staphylococcus aureus*, *streptococcus viridans*, and *streptococcus hemolyticus* intravenously in 11 of the dogs prior to the operation for sclerosing the lymphatics and none of these organisms appeared to have any specificity in producing ulceration of the colon.

IRRITATION BY PANCREATIC JUICE

Portis, Block, and Necheles (52) suggested that ulcerative colitis might be due to an increase in the trypsin content of the colon. An increased motility of the small bowel was thought to be the mechanism by which the trypsin reached the colon before it was destroyed in the ileum. They showed that a 1 to 2 per cent trypsin solution placed in the colon caused damage to the mucosa. Ivy and Clarke (53) however, diverted the bile and pancreatic juice directly into the appendix and colon in six dogs and found no pathological changes in the colonic mucosa during periods varying from six to twenty-three weeks.

This does not preclude the possibility that pancreatic enzymes may serve to irritate ulcers when once formed. That such is not an important factor in some cases of ulcerative colitis is shown by the fact that the ulcers not infrequently remain active when the colon is isolated from the fecal stream by an ileostomy.

VITAMINS

Good evidence is lacking showing that any one of the vitamin deficiencies is associated with ulcers of the colon. For example, Gross (54), who performed complete autopsies on his deficient rats, failed to find that diets deficient in vitamins A, B and C caused ulcers of the colon. He found 6 per cent ulcers of the ascending colon in his control rats and only 3 per cent in his B-deficient rats, though the latter were shown to have considerable intestinal stasis. Tilden and Miller (55) observed ulcerative colitis in 7 of 11 monkeys fed a diet deficient in vitamin A.

EXCRETION OF TOXIC SUBSTANCES

Mercurial colitis is well known to occur when bichloride is given parenterally, and in some cases the small intestine escapes (56). Bismuth is excreted by the colon but without causing ulcers. The parenteral injection of arsenic causes a congestion of the capillaries of the mucosa of the gastrointestinal tract and "rice water stools" and ulcers of the colon and other portions of the alimentary tract may occur (57). Ricin, a poison in castor beans, also causes an enter-

colitis. The only substance which is normally produced in the body and is known to us to produce acute ulcers of the colon is urea in uremic nephritis. These ulcers are thought to be due to the ammoniacal decomposition of urea by bacteria in the colon, and the resulting ammonia is said to be the cause of the irritation and ulceration of the mucosa.

If chronic ulcerative colitis is due to the excretion of some toxic metabolic product, the toxic product if formed by the normal animals must be capable of being excreted elsewhere, since colectomized dogs and monkeys do well for several months if their ileostomy functions well and care is given to the diet; and, of course, colectomized patients may be well indefinitely.

CLINICAL INVESTIGATIONS

Idiopathic or cryptogenic ulcerative colitis, as a disease entity, was described by Wilks (58) in 1875. In the following 35 years, Hale White (59), Gummel (60), Cameron and Ripman (61), Saundby (62), and Hawkins (63) agreed that the disease was distinctive in origin and each suggested a hypothesis regarding its etiology. It appears from the literature that by 1925 many authors considered "chronic ulcerative colitis" to be a distinct clinical entity.

The disease has been variously defined. For example, Herni (64), in 1931 defined it as a "diffuse regional or general inflammation of the colon, especially in its lower part, liable to ulceration, anatomically identical with chronic bacillary dysentery, of uncertain etiology, and possessing no apparent infective properties." Boekus (65) adds to this definition by stating that the disease is "conditioned by varying immunologic, allergic, nutritional, and nervous phenomenon." Paulson (66) defined the disease in a negative manner and states that chronic ulcerative colitis is a "colitis primarily not due to deficiency states, to the administration of metallic products such as mercury, to toxins as in food poisoning, or secondary to known disease. It is not that brought on by an established infectious agent such as the tubercle, dysentery, or chloera bacilli, or by the protozoa Endameba histolytica or possibly Balantidium coli, or by the virus of Lymphogranuloma venereum. It is not that type of colitis seen at autopsy as one of the terminal manifestations of a disease such as nephritis. In short, its etiology is still undetermined, and it cannot even be stated to be a distinct entity. The condition appears as a syndrome, a set of symptoms occurring together and the sum of signs of a morbid state due to one or more unknown factors."

Bargen (67) recognizes 9 types of chronic ulcerative colitis on the basis of pathological and clinical findings and etiology. *Type 1* is called "thrombo-ulcerative colitis". The disease starts in the rectum and sigmoid and ascends and is caused by Bargen's characteristic streptococcus. This type was diagnosed in 66 per cent of his 500 cases. The lesions in *Type 2 and 3* are atypical

in distribution as compared to *Type 1*, the difference between type 2 and 3 being that some of the lesions in Type 3 may be within the reach of the proctosigmoidoscope. A common etiologic agent for Types 2 and 3 has not been found. Types 2 and 3 occurred in 13 per cent of 500 cases. *Type 4* refers to tuberculous ulcers, and *Type 5* to ulcers associated with *Endamoeba histolytica*. *Type 6* refers to a type of colitis in which the mucosa is diffusely hyperemic but not ulcerated except perhaps for very small abrasions, the colon is atonic and puddling of barium occurs. It is considered to be due to dietary deficiency. *Type 7* refers to ulcerations located solely in the rectosigmoid and associated etiologically with venereal lymphogranuloma. *Type 8* refers to cases sometimes diagnosed as "allergic colitis". *Type 9* refers to those cases in which there is a "significant agglutination of one of the *B. dysenteriae* group of organisms".

Bargen's Types 4 and 5 require no discussion. Type 6 requires no discussion, since these patients should respond promptly to vitamin supplementation or an adequate diet. Type 7 could be accepted for those patients in whom the diagnosis of lymphogranuloma venereum is certain. Type 8 certainly applies to those patients who respond to specific allergic management. Type 9 requires no discussion when the bacilli are found and the agglutination titer is relatively high. Controversy arises only when one ascribes a cause to the ulcers under Bargen's Types 1, 2, and 3. The various clinical viewpoints and the reasons prompting them will be briefly indicated without an attempt to cover the entire literature.

Diplostreptococcus. Rafsky and Manheim (68) reported observation on 314 patients with miscellaneous disease of the bowel. Bargen's diplostreptococcus was found in a wide variety of cases and was not specifically limited to ulcerative colitis. They viewed the organism as being a non-specific enterococcus. Paulson (7) and Bassler (69) were also able to isolate the organism from patients with and without chronic ulcerative colitis.

Mones and Sanjuan (8), Felsen (10), Feder (70), Cartwright (71), Lups (144) and Streicher and Kaplan (72) were able to isolate the diplococcus from a variable number of patients with ulcerative colitis. Felsen, for example, wrote that in most cases "the organism corresponded to the enterococcus of Huntoon and McElroy."

Dukes (73), Hurst (74), Hern (64), Brown (75), Gaither (76) and others have expressed the opinion that the diplococcus and other organisms, with the exception in some cases of *B. dysenteriae*, are secondary invaders. This is a possibility which may always obtain under any conceivable experimental condition because of the constant exposure of the colon to bacteria.

Many authors have reported that an upper respiratory infection frequently precedes the first attack or a relapse of the disease. Bargen, Jackman and

Kerr (77) have supplied the most data on "predisposing factors". In 871 cases of relapse the predisposing factor was undetermined in 650 cases; in the remaining 221 cases, an upper respiratory infection and a focal infection was the predisposing factor in 170 cases. This does not help much because the number of respiratory infections the patients had during a remission which was not followed by a relapse is not recorded.

B. dysenteriae. In 1921, Hurst (78) revived the view of Saundby (62) and Hawkins (63) that chronic ulcerative colitis is a chronic form of bacillary dysentery. Dudgeon (79) isolated Flexner's bacillus from an ulcer of the colon, the swabbings being obtained through a sigmoidoscope. Fletcher and Jepps (80) (1924) reported that carriers, when carefully examined, may show "pus pits" which contain the dysentery bacilli. Hurst (81) reports two cases from which Hodfield and Knott had isolated Flexner's bacillus from ulcers through a sigmoidoscope. Thorlakson (82) similarly isolated the organism in 4 out of 5 cases. Mackie (83) reviewed the literature and presented an excellent discussion of the relation of chronic bacillary dysentery to chronic ulcerative colitis. He was able to recover dysentery bacilli from 20 per cent of 83 cases considered to have chronic ulcerative colitis. He concluded that the evidence does not warrant a unitary theory of the cause of chronic bacillary dysentery. Felsen (84) has reviewed the literature on this subject up to 1944. A survey of this literature shows that a form of *B. dysenteriae* has been found in from 2 to 60 per cent of patients with chronic ulcerative colitis.

A number of authors have followed groups of patients who have had bacillary dysentery. Felsen (85) has presented the results of a study of the relation of a history of or exposure to bacillary dysentery. He provided a list of 85 patients with chronic ulcerative colitis. Among these, 8 were derived from an epidemic of dysentery which occurred in New Jersey and came probably from a group of 122 patients which he followed for 9 to 12 months; that is, 8 of 122 patients (6.5 per cent) known by him to have had dysentery manifested a chronic ulcerative condition of the colon 1 year after the acute attack. Cultures and bacteriophage were not reported on these cases at 1 year; positive agglutinations are reported on 5 of the 8 cases. Brown and Bargen (86) have reported a 17 year follow up study on 140 cases of bacillary dysentery occurring in an epidemic in Minnesota in 1921, only one case developed chronic ulcerative colitis. Other studies of a similar nature reviewed by Penner (87) and Felsen (84) indicate that "chronic colitis" occurs in from less than 1 per cent up to 10 per cent. When the organism is found one cannot be certain on the basis of existing evidence whether its presence represents a carrier state, a reinfection, or a direct cause of chronic ulcers.

It seems to be well established that some cases of chronic ulcerative colitis are related to and perhaps due to the dysentery bacillus. But, as Penner

(87), Hern (64), Mackie (83) and other have pointed out, certain criteria are lacking to prove that bacillary dysentery and most cases of chronic ulcerative colitis have a common etiology. These criteria have been listed by Bargen, Copeland and Buie (88) as follows: 1) isolation of *B. dysenteriae* in all cases—this is difficult to do even in epidemic cases of bacillary dysentery; 2) positive agglutinations—these are found in normal individuals occasionally and sometimes not even in proven cases of bacillary dysentery; 3) presence of bacteriophage—this is also sometimes found in normal individuals and not in epidemic cases of bacillary dysentery; 4) proper incidence of disease—the age and sex incidence of these two diseases appear to be different; in bacillary dysentery the age incidence is common in a younger age group (infancy and childhood) and is equally distributed between the sexes. Ulcerative colitis, however, is a disease of the third and fourth decades and appears to be twice as common in females as males. 5) Epidemic history is inconclusive—bacillary dysentery is markedly infective, whereas one must search long to find more than one case of ulcerative colitis in a family.

Serum and vaccine therapy as related to etiology. It is difficult to use therapeutic results in the case of chronic ulcerative colitis for ascertaining their relation to etiology. Other therapeutic measures are always used, when a serum or vaccine is employed, and it is difficult prognostically to grade patients; and, we have found no report in the literature in which a significantly large number of patients have been alternated between the use and non-use of a serum, the management being otherwise the same. As we interpret the literature, approximately the same therapeutic results have been reported for the Bargen-Logan serum (89), poly-valent antidysertery serum (84, 90), antitoxic *B. coli* serum (91) and typhoid vaccine (92).

In this connection, regardless of the cause of the initial stage of the disease (specific streptococcus, bacillary or amoebic dysentery, a metabolic disturbance, etc.), as the disease progresses and the deeper layers of the colon become involved, the bacteria in the deeper tissues may become facultative. Bacteria on the surface of the ulcers may not be representative of those growing in the deeper tissues.

B. morgani. *B. morgani* has been thought by some to be an organism which may cause diarrhea and dysentery in man and animals. T. Lyötta (93) suspected that it might be concerned in the genesis of ulcerative colitis. However, Gardner (9), who has reviewed the literature on the subject, states that there is "no conclusive evidence that the organism is the cause of intestinal disturbance or any other disease in man." He suspects that its presence in relation to epidemics of diarrhea is coincidental. The pathogenic significance of the organism is questioned also by Pulaski and Deitz (94).

Amebiasis. A number of authors (95, 96) have suggested that chronic

ulcerative colitis may be, at least in some cases, a disease which develops secondary to amebiasis. Reed (97) reports that 25 per cent of his 35 cases had antecedent amebiasis.

Keifer (98) applied the Craig complement-fixation test for amebiasis to ulcerative colitis cases and found that fifteen out of nineteen cases showed three plus to four plus reactions to the test. He does not draw any conclusions but suggests that perhaps chronic ulcerative colitis is a secondary pyogenic infection superimposed upon an original amebic infection. To avoid erroneous results in such work, it would seem to be desirable to make the amebic antigen from cultures containing only one bacterial symbiont, as suggested by Rees (99).

Henderson, Pinkerton, and Moore (100) found a case of histoplasmosis in which the salient feature was ulceration of the colon. They reviewed the literature and found that among the 25 cases reported, 8 showed a similar pathologic involvement. This relatively rare disease can hardly be confused with non-specific chronic ulcerative colitis by those acquainted with its clinical characteristics.

Fungus. As in the case of "peptic" ulcer, moulds have been suspected as etiological agents. For example, Swartz and Jankelson (101) examined 24 patients with ulcerative colitis and a like number of controls. They were able to isolate a fungus in the feces in 87.5 per cent of the patients as compared to 33.3 per cent of their normals. The most common fungus was *Geotrichum* but they also found *Monilia albicans*, as well as unidentified yeast-like organisms. The authors did not claim that these fungi are of etiologic significance but felt that there was a relationship between *Fungus geotrichum* and ulcerative colitis.

Allergy. Andresen in 1925 (102) and again in 1933 (103) stressed the importance of allergy as a cause of ulcerative colitis. In 1942, he reported (104) that 33 of 50 patients (66 per cent) responded to dietary allergic management in such a manner as to lead him to believe that food allergy was the cause of the disease in these patients. He points out, however, that though the acute process may be infectious in some cases the bowel may become secondarily sensitized. The observations of Gray and Walzer and their colleagues (42, 43, 44, 105) indicate that an atopic reagin may be located or fixed in the colonic mucosa, so that the specific allergin acting locally can produce an inflammatory reaction. Rowe (106), using Andresen's management, observed remissions in 7 of 14 cases of chronic ulcerative colitis. Mackie (107) has reported that he obtained evidence of allergic reactions to food in 60 per cent of 200 cases of ulcerative colitis at some time during one cycle of the disease. Rowe and Gray (108) have pointed out that local bacterial allergy may be concerned. Collins and Pritchett (109) failed to find that food allergy was a common cause

of the disease but found that allergic management is apparently helpful in some patients.

Eosinophiles have been reported to be present in the tissue about the ulcers in chronic ulcerative colitis. The same is true of chronic "peptic" ulcer or when local necrosis of tissue occurs (an autogenous protein response). Bercovitz (110) has found eosinophiles in the rectal discharges and smears of swabbings of the ulcers in patients having the disease. A local tissue eosinophilia is not considered to be pathognomonic of an allergic process; it is believed to indicate a healing process after an acute inflammation.

Dietary deficiency. The colitis of War Edema (World War I) was suspected as being due to a dietary deficiency because the bacteriological findings failed to account for it and because it "rarely occurred among well-fed prisoners, though they were exposed to the infection, if this was an infection" (111, 112). Rolleston (113) in 1921 suggested that the colonic mucosa might be invaded by bacteria in the presence of a dietary deficiency. In pellagra, Denton (114) has described in long standing deficiency superficial ulcers, cystic lesions of the mucosa, as well as inflammation. Herzenberg (115) pointed out that the cystic lesions (colitis cystica superficialis) are very characteristic of pellagra and occur only infrequently in sprue.

There is no evidence showing that nutritional deficiency states are primary factors in the genesis of chronic ulcerative colitis. Such states may predispose to the condition and arise secondarily. Mackie (116, 117) found evidence of nutritional deficiency in 62 per cent of 75 patients with the disease. In view of the diarrhea and loss of blood and mucus in the active stage of the disease, and the role that vitamins and proteins play in growth and tissue metabolism, it is essential to keep in mind the possibility of the need of vitamins and proteins by these patients.

A metabolic disturbance. It has been suggested, particularly by Logan (118) and Brown (119), that some unknown metabolic disturbance is concerned and acts by reducing the resistance of the mucosa to infection. Haskell and Cantarow (120) found a relative decrease in diffusible calcium and treated 10 patients with calcium and parathyroid extract and obtained what they considered to be a very favorable response. They expressed the view that the change in the rates of diffusible to non-diffusible calcium is the same in mucous colitis and chronic ulcerative colitis. In this connection Walsh and Ivy (121) found that the more frequently an isolated loop of the colon is irrigated the more calcium is obtained. When the colon was washed once hourly for 8 hours from 17 to 55 mg. of calcium was obtained in the washings. Hence, any factor which increases the secretion of the colon increases the loss of calcium. This is a factor which should be considered in any chronic diarrhea.

NEUROGENIC FACTORS

Psychosomatic. Every physician who has seen more than a handful of patients with ulcerative colitis has observed that in one or more a relapse or an exacerbation of symptoms during the course of the disease has apparently been due to an emotional disturbance. Some authors have analyzed their group of patients in this regard. For example, Bargen, Jackman and Kerr (77) have reported that in 26 (15 per cent) of 170 cases in which some factor was determined, an emotional factor appeared to be the cause of the relapse. C. M. Jones (122) has stated that in two-thirds of 100 patients he observed with ulcerative colitis psychogenic factors were related to the onset of exacerbations of the disease. Feder (70) has noted the relation in 5 of 88 patients.

Psychiatrists who have studied patients with ulcerative colitis have been impressed by the role played by the emotional factor, particularly in relation to relapses and exacerbations of symptoms. Murray (123) reported studies on 12 patients with the disease. All had emotional conflicts, but they may be considered as selected patients. Sullivan (124, 125) studied the psychiatric background in 18 of 25 consecutive patients and found that in 15 of the 18 "emotional disturbances appeared to be of definite etiological significance." He estimated that in 60 per cent of patients emotional disturbances are etiologically significant. Daniels (126) saw 25 cases which were selected to the extent that he was asked to see them for psychiatric study and treatment. In 14 of the 25 (56 per cent) emotional factors were apparently concerned. He reported a prompt response to psychotherapy. Wittkower (127) investigated 40 unselected patients with ulcerative colitis. In 28 of the 40 cases (70 per cent) emotional disturbances were considered to be the precipitating factor. These psychiatrists enumerate such psychogenic factors as constant apprehension, prolonged tension, infantile reaction to fear due to such factors as financial or occupational worry, attachment to a parent or realitive, fear of pregnancy, domestic or love difficulties, forthcoming examinations and immature sexual conflicts. Wittkower reported that such emotional disturbances were more frequent in his patients than in the general population.

In view of these reports it is appropriate to inquire regarding the type of emotional disturbances found in patients with mucous colitis, because this is a disease of the colon which does not appear to progress into ulcerative colitis; or if it does, the cases are so few as to have attracted no attention (128, 129). Bockus, Bank and Wilkinson (130) studied the emotional factors in 50 patients with mucous colitis. They found their patients to be emotionally unstable. During exacerbations all the patients manifested tension and 23 showed depressive symptoms. White, Cobb and Jones (128) made a psychiatric study of 53 patients with mucous colitis (mucoid stools present in about 60 per cent of the cases; some of their cases would be diagnosed as an unstable, irritable,

spastic or dyskinetic colon). Chronic emotional tension was found in 92 per cent. Resentment, anxiety, and guilt were most frequently observed, resentment being present in 92 per cent of the cases. "Instinctual drives", "parental friction", "occupational difficulties", "feelings of obligation", are some of the types of conflicting forces which caused the resentment, anxiety or guilt. Thus, we find practically the same types of emotional disturbances listed for patients with chronic ulcerative colitis. The literature also reveals that resentment, anxiety and guilt are reported to be characteristic also of patients with peptic ulcer.

If these emotional factors are etiologically concerned in the three diseases, why do they affect the stomach in some persons, cause mucous colitis in others, and in still others, as some believe, cause ulcerative colitis? Anxiety must affect, we shall assume, the colonic nuclei of the hypothalamus in some and the gastric nuclei in others, and in others both. Either the nervous centers are differentially affected by anxiety or there is a difference in the susceptibility of the stomach and colon to parasympathetic effects in different persons. If anxiety is present in patients with mucous colitis and in patients with ulcerative colitis, and mucous colitis does not progress to ulcerative colitis, some additional factor is present in the latter condition. In the presence of the etiological background of chronic ulcerative colitis, it is not difficult to understand why a patient, whose colon is responsive to anxiety, will suffer an exacerbation of symptoms.

Effect of nerves on blood supply of the colonic mucosa. It has been found that fright or exercise will cause blanching of the colonic mucosa of dogs (131, 132, 133). White and Jones (134) observed blushing of the colonic mucosa in human subjects when they were embarrassed. Stimulation of the sympathetic supply of the colon caused blanching and of the parasympathetic caused blushing, congestion or blanching depending on the degree of contraction of the muscularis (133).

Of course, irritants, allergins, and vasoconstrictor and dilator drugs applied directly to the mucosa cause marked changes in the blood flow (134) of the mucosa.

Effect of nerves on secretion by the colon. The literature on this subject was reviewed by Florey, Wright and Jennings in 1941 (135). Only several points of clinical interest will be mentioned. Irritants and cholinergic drugs applied locally cause the secretion of a thick mucus. Prolonged stimulation of the pelvic nerves in the cat causes the secretion of a considerable amount of mucoid fluid, and its secretion is influenced reflexly in cat and man (136). Atropine and barbiturates in effective doses reduce or abolish the secretion due to nervous effects but not local irritants.

The effect of muscular spasm on the mucosa. The functional innervation of

the colon has been reviewed by Alvarez (177, 138, 139). There is no doubt regarding the observation that anxiety affects the motility of the colon in many persons, causing a general increase in motility; localized or general hypertonus, or incoordination between segments. There is no doubt that in lower animals the appropriate stimulation of the pelvic nerves (*N. erigentes*) will cause a contraction of the rectum and distal colon, and that, though variations are encountered, the sympathetics are predominantly motor.

Lium (23) has shown, as might be expected from similar experiments on the stomach, that marked contraction of the colonic musculature may cause erosions or acute ulcers of the mucosa. These lesions healed quickly. Lium and Porter (140) in addition studied the location of ulcers in 6 patients who died with ulcerative colitis and found that they were located in the rectum, as well known, and preferentially along the tenial bands in the sigmoid and descending colon. This indicates that muscular contractions has a localizing effect but not necessarily an etiological effect in chronic ulcerative colitis. If spasm and dyskinesia is a cause of acute ulcers of the colon clinically, it is surprising that more are not seen by proctoscopy in patients with diarrhea, mucous colitis, and "spastic colon".

No one has stimulated the pelvic nerves or the hypothalamus over a prolonged period to ascertain if chronic ulcers of the colon will occur. It is plausible to suspect that excessive motility and tone of the colon would be a factor operating to maintain acute lesions and to cause them to become chronic. Regardless of the suggestions of Evans (141), Drueck (142), Kuttner (143) and others, there is certainly a paucity of evidence indicating that chronic ulcerative colitis is a late stage of functional dyskinesia of the colon.

SUMMARY

Acute lesions of the colon have been produced by the intravenous injection of diplostreptococci, streptococci, *B. coli*, *B. dysenteriae*, and presumably a virus. Only one investigator, namely Cook, has presented rather decisive evidence that acute ulcers of the colon may be produced, maintained and relapses elicited on an infectious basis, the organism apparently being the diplo-streptococcus of Bargen.

The observations of Cook are challenging and merit repetition; in addition, other organisms, including *B. dysenteriae* and the virus of Mones, should be used to ascertain whether a disease simulating chronic ulcerative colitis may be produced in animals. The observations on *B. necrophorum* suggest that they may be responsible for maintaining the chronicity of lesions of the colon, but this has not been tested by producing acute lesions and directly infecting them with the organism.

Mechanical trauma of the mucosa or vascular injuries caused by contraction

of the muscularis, or vascular injuries caused by capillary poisons may cause acute lesions of the colon. Since these appear to heal rapidly, attempts should be made to discover factors which will cause acute lesions to become chronic.

Ulcers have been produced experimentally by injecting sclerosing substances into the lymphatic supply of the colon.

Acute ulcers of the colon have been produced on an allergic basis. Such ulcers have not been shown to remain chronic. It is not known how to maintain allergic ulcers in a chronic state.

Irritation of acute ulcers of the colon by pancreatic juice may constitute a chronicity factor, though this has not been clearly demonstrated. A deficiency of vitamins may be a chronicity factor. Acute ulcers of the colon have been observed to a significant extent only in the monkey in high grade Vitamin A deficiency. It has not been shown that chronic ulcers of the colon may be produced by the excretion of toxic substances by the mucosa of the organ.

Clinically it is clear that chronic ulcers of the colon may occur in tuberculosis, amebiasis, bacillary dysentery, in high grade dietary insufficiency, and in the early stages of venereal lymphogranuloma. It seems also certain that bacillary dysentery and amebiasis may in some cases antedate cryptogenic chronic ulcerative colitis. It does not appear to have been established that bacillary dysentery is the cause of most cases of chronic ulcerative colitis. Local allergy may be a factor in the genesis and chronicity of ulcers of the colon in some cases and should be considered in the management of the disease. It would appear that in most cases of chronic ulcerative colitis nutritional deficiency is secondary. There is no evidence indicating that the disease is due to a disturbance of the excretory function of the colon or some specific metabolic disorder. Though emotional disturbances (anxiety, resentment, guilt) are concerned in the exacerbation of symptoms and in some cases are related to the onset and relapses of the disease, there is a paucity of evidence showing that chronic ulcerative colitis is a late stage of mucous colitis, of functional dyskinesia of the colon, or of some subtle vascular or neurotropic disturbance. If such emotional disturbances are etiologically concerned, they cannot be the sole factor, since they are also thought to be concerned also in the genesis of peptic ulcer and other "chronic" diseases.

BIBLIOGRAPHY

1. BARGEN, J. A.: J. A. M. A., 83: 332, 1924.
2. BARGEN, J. A., AND LOGAN, A. H.: Arch. Int. Med., 36: 818, 1925.
3. BUTTIANUX, R., AND SEVIN, A.: Ann. Inst. Pasteur, 47: 173, 1931.
4. COOK, T. J.: J. Am. Dent. A., 18: 2290, 1931.
5. PAULSON, M.: Arch. Int. Med., 41: 75, 1928.
6. BUIE, L. A., AND BARGEN, J. A.: J. A. M. A., 101: 1462, 1933.
7. PAULSON, M.: J. A. M. A., 101: 1687, 1933.

103. ANDRESEN, A. F. R., AND D'ALBORA, J. B.: M. Times and Long Island M. J., October, 1933.
104. ANDRESEN, A. F. R.: Am. J. Digest. Dis., 9: 91, 1942.
105. WALZER, M., GRAY, J., AND HARTEN, M.: Ann. Int. Med., 13: 11, 1940.
106. ROWE, A. H.: Ann. Int. Med., 17: 83, 1942.
107. MACKIE, T. T.: Am. J. Digest. Dis., 9: 97, 1942.
108. GRAY, I.: Am. J. Digest. Dis., 9: 97, 1942.
109. COLLINS, E. N., AND PRITCHETT, D.: M. Clin. North America, 22: 297, 1938.
110. BERCOVITZ, Z.: Am. J. Digest. Dis., 9: 97, 1942.
111. PARK, F. S.: J. A. M. A., 70: 1826, 1918.
112. OBERNDORFER, H.: München med. Wchnschr., 65: 119, 1918.
113. ROLLESTON, HUMPHREY: Lancet, 204: 939, 1923.
114. DENTON, J.: Am. J. Trop. Med., 15: 173, 1925.
115. HERZENBERG, H.: Beitr. z. Path. u. path. Anat., 96: 97, 1935.
116. MACKIE, T. T.: J. A. M. A., 104: 175, 1935.
117. MACKIE, T. T., EDDY, W. H., AND MILLS, M. A.: Ann. Int. Med., 14: 28, 1940.
118. LOGAN, A. H.: Northwest Med., 18: 1, 1919.
119. BROWN, T. R.: Ann. Clin. Med., 4: 425, 1925.
120. HASKELL, B., AND CANTAROW, A.: Am. J. M. Sc., 181: 180, 1931.
121. WALSH, E. L., AND IVY, A. C.: Proc. Soc. Exper. Biol. & Med., 25: 839, 1927-28.
122. JONES, C. M.: Am. J. Digest. Dis. & Nutrition, 2: 656, 1935-36.
123. MURRAY, C. D.: Am. J. M. Sc., 180: 239, 1930.
124. SULLIVAN, A. J., AND CHANDLER, C. A.: Yale J. Biol. & Med., 4: 779, 1932.
125. SULLIVAN, A. J.: Am. J. Digest. Dis. & Nutrition, 2: 651, 1936.
126. DANIELS, G. E.: New England J. Med., 226: 178, 1942.
127. WITKOWER, E.: Brit. M. J., 2: 1356, 1938.
128. WHITE, B. V., COBB, S., AND JONES, C. M.: Psychosomatic Medicine Monograph, National Research Council, 1939.
129. BARGEN, J. A.: National Med. Monographs, National Medical Book Co. Inc., N. Y., 1935.
130. BOCKUS, H. L., BANK, J., AND WILKINSON, S. A.: Am. J. M. Sc., 176: 813, 1928.
131. DRURY, A. N., FLOREY, H., AND FLOREY, E.: J. Physiol., 68: 173, 1929.
132. BARCROFT, J., AND FLOREY, H.: J. Physiol., 68: 181, 1929.
133. IVY, A. C.: Unpublished data.
134. WHITE, B. V., AND JONES, C. M.: New England J. Med., 218: 791, 1938.
135. FLOREY, H. W., WRIGHT, R. D., AND JENNINGS, M. A.: Physiol. Rev., 21: 36, 1941.
136. LARSEN, L. M., AND BARGEN, J. A.: Arch. Surg., 27: 1120, 1933.
137. ALVAREZ, W. C.: Introduction to Gastroenterology, P. B. Hoeber, New York, 1939.
138. GARVEY, R. C.: Physiol. Rev., 14: 103, 1934.
139. WEILS, J. A., MERCER, T. H., GRAY, J. S., AND IVY, A. C.: Am. J. Physiol., 138: 83, 1942.
140. LIUM, R., AND PORTER, J. E.: Am. J. Path., 15: 73, 1939.
141. EVANS, W. A., JR.: New England J. Med., 210: 743, 1934.
142. DRUECK, C. J.: Internat. Clin., 3: 85, 1929.
143. KUTTNER, H.: Deutsche med. Wchnschr., 52: 762, 1926.
144. LUPS, S.: Vaccine Therapy in Ulcerative Colitis, J. B. Walter, Groningen, Holland, 1934, for abstract see Am. J. Digest. Dis., 2: 65, 139, 1935-36.

SOME RESULTS OF THE GASTRIC SECRETORY RESPONSE OF PATIENTS HAVING DUODENAL ULCER NOTED DURING THE ADMINISTRATION OF BENADRYL

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INTRODUCTION

For many years it has been known that histamine is a substance which causes a rapid and prolonged elevation of the acid gastric secretory rate. Indeed it has been accepted as one of the most powerful of gastric secretagogues. The increased tendency for peptic ulcer to develop, or to become reactivated, in the presence of accentuated gastric acidity is accepted by most physiologists. Knowledge of these facts leads naturally to the hope that a drug possessing antihistamine properties may be of some use in the treatment of peptic ulcer. There has been an active search for a compound which, though relatively nontoxic, possesses the ability to block the action of histamine. Thymoxyethydiethylamine (929F) and N-diethylaminoethyl-N-ethylaniline (1571F) are two drugs which possess a powerful antihistamine effect (1). The effect of these drugs on gastric secretion has been studied (2, 3); 929F does not diminish the secretory response of Heidenhain pouches in dogs to histamine but both 929F and 1571F usually inhibit the secretory response of gastric pouches in dogs to the ingestion of a test meal. These two compounds, however, are toxic and the margin between toxic manifestations and antihistamine activity is narrow; therefore they do not lend themselves to clinical application (4).

A drug called "benadryl" which possesses certain antihistamine properties, has been synthesized in the laboratories of Parke, Davis & Company. The chemical name of the compound is beta-dimethylaminoethyl benzhydryl ether hydrochloride. Loew, Kaiser and Moore (5) published the first report dealing with this new drug. They found it to be relatively nontoxic and noted that it possesses, in high degree, the ability to protect guinea pigs against the bronchoconstriction induced by atomized histamine. They suggested that this drug may have experimental and clinical application in problems dealing with the rôle of histamine in gastric secretion, vasodilatation, capillary permeability, mediation of pain, smooth muscle spasm and various allergic syndromes.

Reports have already appeared which suggest that benadryl may be a useful drug in the control of certain allergic states (6-8). McElin and Horton (9) studied the effect of benadryl on the gastric response to histamine of patients having multiple sclerosis. These workers noted that in four of the cases

studied, benadryl had some ability to block the gastric response and stated that their observations suggest that benadryl depresses the gastric response to histamine. These reports led us to undertake a study of the effect of the drug on the gastric response of patients having duodenal ulcer. We hoped to determine if possible whether or not one was justified in expecting that benadryl, because of its ability to prevent some of the actions of histamine, might have an inhibitory effect on gastric secretion and thereby prove to be of use in the treatment of peptic ulcer.

We wish to report some observations of the effect which, in our hands, benadryl has exerted on the gastric secretory response of patients having duodenal ulcer.

MATERIAL FOR STUDY

Sixteen patients were studied. Fifteen of these had duodenal ulcer proved by roentgenogram. One patient had a clinical history characteristic of duodenal ulcer but a roentgenogram failed to demonstrate such a lesion. The duration of symptoms ranged from one to thirty years. There were eleven men and five women, ranging in age from thirty-three to sixty years. All were hospital patients who were receiving recognized standard diets for treatment of ulcer. All patients were fasting at the time the observations were begun.

Group 1.—Rivers, Osterberg and Vanzant (10) showed that successive equal subcutaneous injections of histamine produced almost identical curves of gastric acid response. This was designated the "double histamine test." Its graphic representation produced a "tandem" type of curve. If in the original double histamine test the two curves are similar, subsequent examinations performed within a few days usually exhibit similar characteristics in both curves. If tested material injected between the two injections of histamine changes the behavior of the second or expectancy curve it is suggestive that such a substance is probably causative in changing the second curve. This double histamine method was employed in studying four patients. In three cases the test was performed as a control the day prior to administration of benadryl. In each case practically identical curves of gastric concentration were obtained.

As the stimulating dose 0.04 mg. of histamine base per 10 kilograms of body weight was selected, because it caused an adequate rise of secretion of gastric acid and yet it was not so large as to give untoward side reactions. On the morning of the study a gastric tube of small lumen was introduced into the stomach. Several fasting specimens of gastric contents were obtained. Histamine was then injected subcutaneously and specimens of the gastric contents were collected at intervals of ten minutes until the gastric acidity had returned to the fasting level. Intravenous administration of 60 mg. of benadryl in 100

cc. of isotonic saline solution flowing at a rate of 25 to 30 drops per minute was then begun, the injection being made into the antecubital vein of either arm. A second subcutaneous injection of histamine was then given and specimens of gastric contents again were collected at intervals of ten minutes, during the period of administration of benadryl, until the gastric acidity had returned to normal. In the fourth case the dose of histamine was reduced to 0.02 mg. of histamine per 10 kilograms of body weight and the dose of benadryl was increased to 200 mg. in 250 cc. of isotonic saline solution flowing at a rate of 25 to 30 drops per minute.

In these cases the concentration of free hydrochloric acid in the gastric secretion obtained was not lessened; rather it was slightly increased when benadryl was being administered at the time histamine was given, when this

TABLE I
Gastric secretory responses in group I

CASE	HISTAMINE GIVEN SUBCUTANEOUSLY		HISTAMINE GIVEN SUBCUTANEOUSLY WITH SIMULTANEOUS INTRAVENOUS ADMINISTRATION OF BENADRYL SOLUTION	
	Maximal free hydrochloric acid degrees	Total volume of gastric contents cc.	Maximal free hydrochloric acid degrees	Total volume of gastric contents cc.
1*	90	455	94	265
2*	100	550	127	540
3*	91	670	98	600
4†	75	60	100	60

* The patients were given 0.04 mg. of histamine per 10 kilograms of body weight and 60 mg. of benadryl.

† The patient was given 0.02 mg. of histamine per 10 kilograms of body weight and 200 mg. of benadryl.

is compared to the response following the administration of histamine alone. In two cases only was the volume of the gastric contents appreciably lower during the administration of benadryl. Table 1 is a summary of the gastric secretory responses in these four cases. Figure 1 is a representative case.

Group 2.—To three patients a dilute solution of histamine was given into the antecubital vein by the slow drip technic. In two of the cases 1 mg. of histamine base in 250 cc. of isotonic saline solution (0.0004 per cent solution) was employed. In the third case 0.5 mg. of histamine base in 250 cc. of isotonic saline solution (0.0002 per cent solution) was employed. Several fasting specimens of gastric contents were first collected. Administration of the solution of histamine was then begun. The solution was permitted to run at a rate of 30 to 35 drops per minute and specimens of gastric contents were collected at intervals of ten minutes thereafter until the end of the observa-

tions. Care was taken to empty the stomach as nearly as possible with each collection. After the curve of acid concentration appeared to have reached its peak, 60 mg. of benadryl in 100 cc. of isotonic saline solution were administered by the intravenous drip technic at a rate of 25 to 30 drops per minute into the antecubital vein of the opposite arm, without interrupting the administration of the histamine. The concentration of the free hydrochloric acid in the gastric secretion obtained was maintained at its maximum during the administration of benadryl. In only one case was the volume of gastric contents

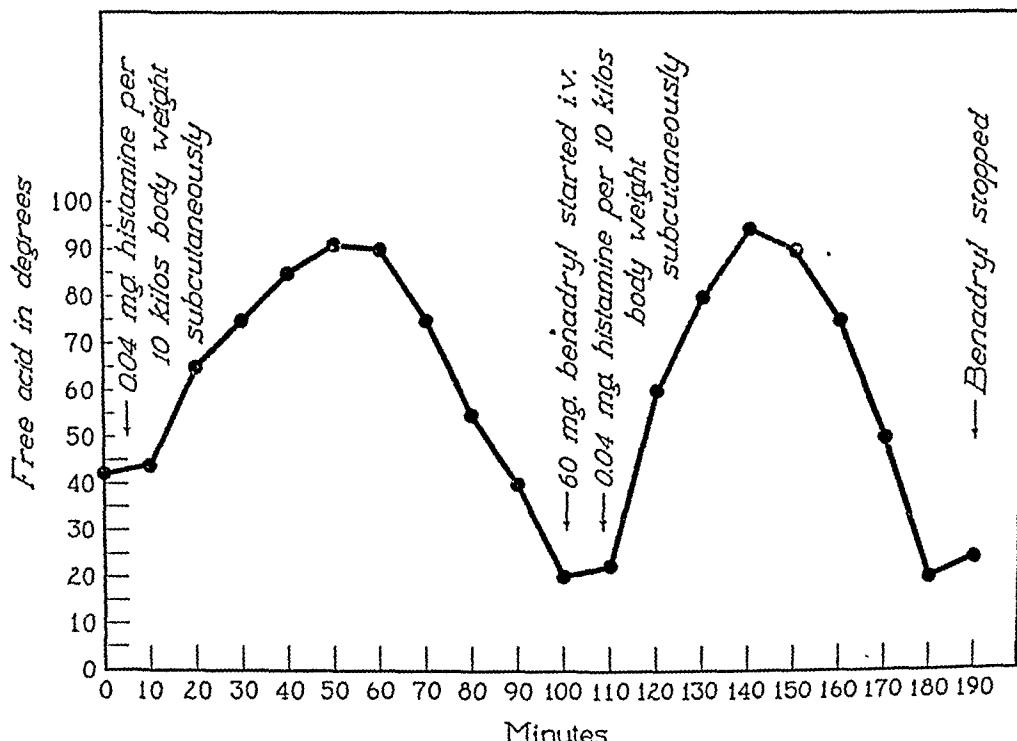


FIG. 1. EFFECT OF BENADRYL ON REACTION OF GASTRIC ACIDITY TO SUBCUTANEOUS ADMINISTRATION OF HISTAMINE

lowered appreciably during the administration of the benadryl. Table 2 shows results in these three cases. Figure 2 is a representative case.

Group 3.—To three patients we administered test meals consisting of eight arrowroot cookies and two glasses of water rather than using histamine stimulation. One hour after the ingestion of the meal a gastric tube of small lumen was introduced into the stomach and specimens of gastric contents were collected at intervals of ten minutes for one hour. In each case we attempted to empty the stomach completely at the end of one hour. We then administered 100 mg. of benadryl in 200 cc. of isotonic saline solution by the intravenous slow drip technic into the antecubital vein of either arm at a rate of 35 to 40 drops per minute. Thirty minutes after administration of benadryl had been

begun and without interrupting the administration of the drug, a second test meal was given. In one hour thereafter a gastric tube was reintroduced into

TABLE 2
Gastric secretory responses in group 2

CASE	HISTAMINE GIVEN INTRAVENOUSLY		HISTAMINE AND BENADRYL GIVEN INTRAVENOUSLY	
	Maximal free hydrochloric acid degrees	Total volume collected during 1 hour cc.	Maximal free hydrochloric acid degrees	Total volume collected during 1 hour cc.
1*	120	195	125	200
2*	96	295	116	280
3†	112	115	119	84

* The patients were given 0.0004 per cent solution of histamine.

† The patient was given 0.0002 per cent solution of histamine.

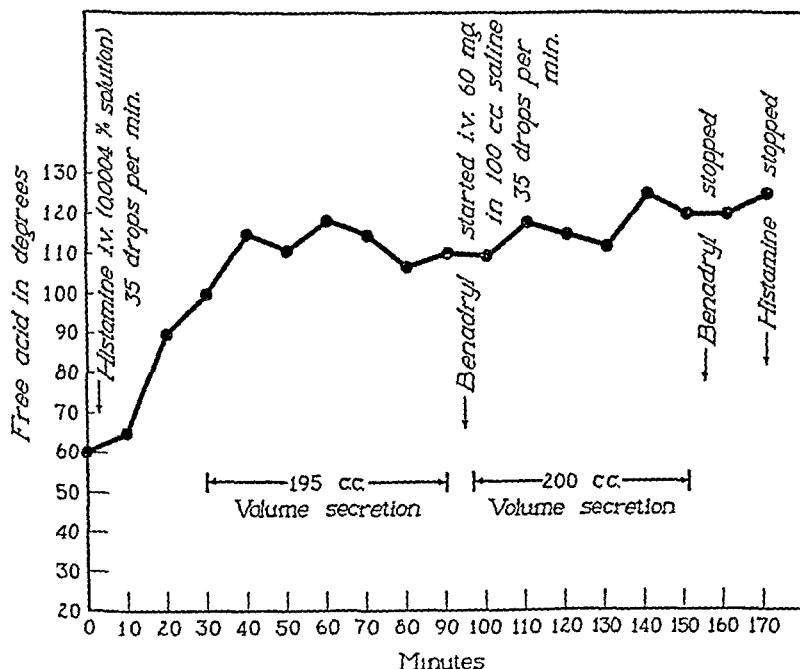


FIG. 2. EFFECT OF BENADRYL ON REACTION OF GASTRIC ACIDITY AND VOLUME OF GASTRIC SECRETION TO INTRAVENOUS ADMINISTRATION OF HISTAMINE

the stomach and specimens of gastric contents were collected at intervals of ten minutes for an hour.

In these three cases we noted an unexplained slight to moderate increase

of the concentration of the free hydrochloric acid in the gastric secretion obtained, following the test meal given, during the period of administration of the benadryl solution as compared to the response following the test meal

TABLE 3
Gastric secretory responses in group 3

CASE	TEST MEAL* ALONE		BENADRYL AND TEST MEAL	
	Maximal free hydrochloric acid degrees	Total volume of gastric contents during 1 hour cc.	Maximal free hydrochloric acid degrees	Total volume of gastric contents during 1 hour cc.
1	55	135	59	110
2	35	90	65	90
3	68	70	80	35

* Test meal = eight arrowroot cookies and two glasses of water.

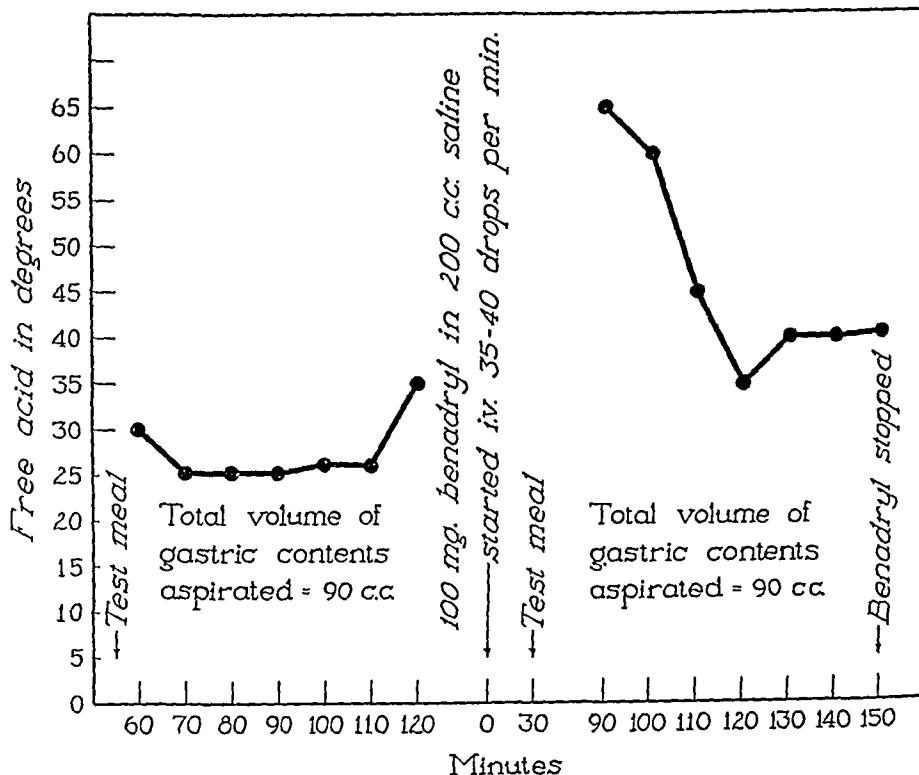


FIG. 3. EFFECT OF BENADRYL ON REACTION OF GASTRIC ACIDITY AND VOLUME OF GASTRIC SECRETION TO INGESTION OF A TEST MEAL

given at the beginning of the observations. In two cases the volume of the gastric contents was reduced following the second test meal as compared with that induced by the first test meal. Table 3 shows the results obtained in this group of cases. Figure 3 is a representative case.

As a control to this study two of the patients were studied by giving two consecutive test meals of eight arrowroot cookies and two glasses of water on the same day without the administration of benadryl. The second test meal was given when the concentration of gastric acid stimulated by the first test meal had fallen to the fasting level. In both cases we found that the rise in the concentration of the gastric acid and the volume of gastric secretion, after the second test meal, did not differ materially from the values obtained after the first test meal.

Group 4.—Six patients were studied using test meals of eight arrowroot cookies and two glasses of water. One hour after the test meal was given, a gastric tube of small lumen was introduced into the stomach and the entire gastric contents were aspirated. The volume and the concentration of the free hydrochloric acid of the gastric contents were noted in each case. Intravenous

TABLE 4
Gastric secretory responses in group 4

CASE	TEST MEAL* ALONE		BENADRYL AND TEST MEAL	
	Free hydrochloric acid concentration	Total volume of gastric contents	Free hydrochloric acid concentration	Total volume of gastric contents
1	degrees 40	cc. 110	degrees 40	cc. 170
2	50	175	52	160
3	77	90	69	170
4	65	125	40	100
5	46	175	15	175
6	22	160	30	150

* Test meal = eight arrowroot cookies and two glasses of water.

administration of 200 mg. of benadryl in 200 cc. of isotonic saline solution was then begun at a rate of 35 to 40 drops per minute. One half hour after beginning the administration of benadryl, and without interrupting its administration, a second test meal was given. One hour later the entire gastric contents were aspirated and again the free hydrochloric acid concentration and volume of the gastric contents were noted in each case.

In three of these cases the test meal given during the administration of the benadryl failed to stimulate a gastric secretion whose free hydrochloric acid concentration was as high as that produced by the test meal given before the administration of the benadryl. In two cases the difference was moderate in degree; in one it was slight. In the remaining three cases, on the other hand, the free hydrochloric acid concentration of the gastric contents after the second test meal was equal to or slightly greater than that of the gastric contents following the first meal. No consistent alteration of the total volume of gastric

secretion aspirated was noted following the test meals given before the administration of benadryl as compared with that received following the second test meal.

Table 4 shows the results in these cases. Figure 4 is representative of the group.

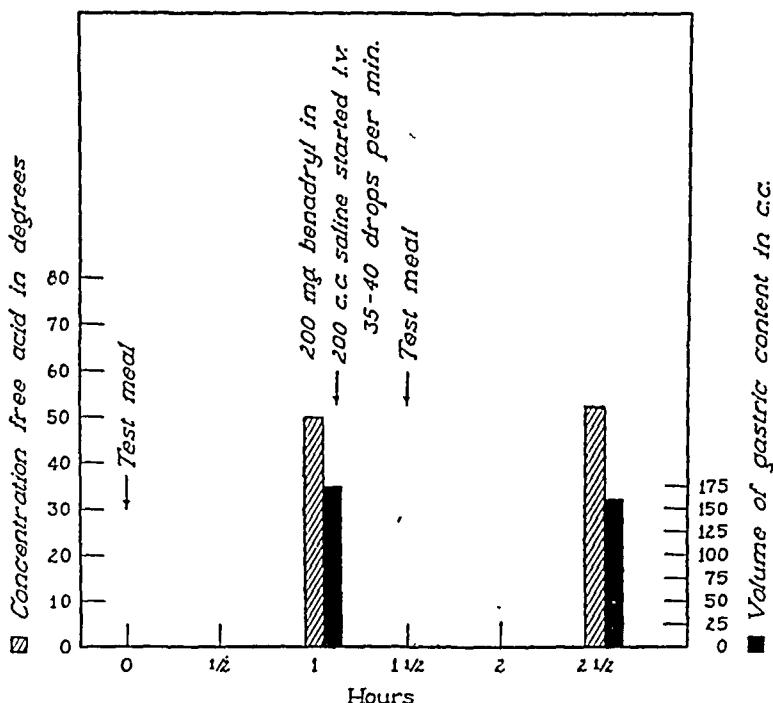


FIG. 4. EFFECT OF BENADRYL ON REACTION OF GASTRIC ACIDITY AND VOLUME OF GASTRIC SECRETION TO INGESTION OF A TEST MEAL

COMMENT

We did not accurately measure the total volume of gastric secretion in this study. The figure recorded as representing the total volume of gastric contents is the volume of gastric contents that could be aspirated from the stomach during the course of an analysis. We feel, however, that this figure has comparative value and is worth mentioning.

In the cases in which histamine was used as a stimulant of gastric secretion no reduction in the concentration of free hydrochloric acid and no consistently significant reduction in the total volume of secretion followed the intravenous administration of benadryl. A similar result was noted in the majority of the cases in which a test meal of arrowroot cookies and water was used as a stimulant of gastric secretion. Indeed in the entire study of sixteen cases the acidity increased after the use of benadryl in all but four cases; the volume of

gastric secretion can be said to have been significantly reduced in only six cases.

The number of cases studied is small, but the results are so consistent that they can probably be accepted as significant. Our findings do not encourage us to believe that benadryl will prove useful in the treatment of peptic ulcer.

REFERENCES

1. HALLENBECK, G. A.: Am. J. Physiol. 139: 329, 1943
2. LOEW, E. R., AND CHICKERING, O.: Proc. Soc. Exper. Biol. & Med. 48: 65, 1941.
3. BURCHELL, H. B., AND VARCO, R. L.: J. Pharmacol. & Exper. Therap. 75: 1, 1942.
4. CODE, C. F.: Proc. Staff Meet., Mayo Clin. 20: 439, 1945.
5. LOEW, E. R., KAISER, MARGARET E., AND MOORE, VERNON: J. Pharmacol. & Exper. Therap. 83: 120, 1945.
6. O'LEARY, P. A., AND FARBER, E. M.: Proc. Staff Meet., Mayo Clin. 20: 429, 1945.
7. KOELSCH, G. A., PRICKMAN, L. E., AND CARRYER, H. M.: Proc. Staff Meet., Mayo Clin. 20: 432, 1945.
8. WILLIAMS, H. L.: Proc. Staff Meet., Mayo Clin. 20: 434, 1945.
9. MCELIN, T. W., AND HORTON, B. T.: Proc. Staff Meet., Mayo Clin. 20: 417, 1945.
10. RIVERS, A. B., OSTERBERG, A. E., AND VANZANT, F. R.: Am. J. Digest. Dis. 3: 12, 1936.

CLINICAL OBSERVATIONS ON THE USE OF BENADRYL: ITS EFFECT ON HISTAMINE-INDUCED GASTRIC ACIDITY IN MAN

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INTRODUCTION

Benadryl (beta dimethylaminoethyl benzhydrol ether hydrochloride), is a new antihistamine substance submitted by Parke, Davis and Company for clinical trial. It is a white crystalline powder, soluble in water and alcohol, and may be slightly opalescent. It is stable under ordinary conditions of temperature and pressure. It is similar to compounds 929F and 1571F (1, 2, 3) of the Fourneau series synthesized by Bovet and Staub at the Pasteur Institute.

We have reported elsewhere (4) concerning the use of benadryl in the treatment of more than 100 patients whose symptoms were thought to be the result of release of histamine or histamine-like substance. In that report, a brief summary of our observations concerning the clinical pharmacology of this drug was presented and the antagonism of benadryl to certain of the well-known clinical effects of histamine was evaluated. We were particularly interested in the ability of benadryl to inhibit the gastric acid response induced in human subjects by the parenteral administration of histamine, and submitted the opinion that there was suggestive evidence that benadryl opposed in some measure the rise of histamine-induced gastric acidity in subjects with multiple sclerosis.

This communication represents a more detailed report of our preliminary gastric studies with particular emphasis on the dilutions and quantities of histamine and benadryl used and the technic of administering these substances.

It is an interesting sidelight that our early gastric studies were abandoned because benadryl seemed so little able to inhibit what appeared to be the almost inevitable rise of both free and combined gastric acids when histamine was administered. The analyses were not resumed until some of the clinical results were so satisfactory that we returned to basic pharmacologic investigation. We then proceeded with the hypothesis that the ability of an antihistamine preparation to antagonize histamine might depend on the relative amounts of the two substances used. As a consequence of this position we changed our technic often. We progressively decreased the amount of histamine given to

the patient, and simultaneously increased the amount of benadryl, until the most common toxic manifestation of drowsiness became unduly manifest. We were endeavoring to ascertain the smallest amount of histamine which would provoke a rise of gastric acidity in order that we might more easily determine if benadryl had any effect in opposing the action of histamine. When the fact is accepted that the dosage of histamine used in the ordinary histamine test meal is far in excess of the amount needed to provoke a measurable rise in gastric acidity, the possibility presents itself that benadryl might conceivably oppose histamine in amounts liberated in the human body. It must be kept

TABLE 1
Dilution of histamine used in eighteen analyses of gastric content

SOLUTION	METHOD OF ADMINISTRATION	NUMBER OF TIMES USED
1:250,000 (1.0 mg. of histamine base per 250 cc. physiologic saline solution)		6
1:500,000 (1.0 mg. of histamine base per 500 cc. physiologic saline solution)	Continuous intravenous drip method	1
1:1,000,000 (1.0 mg. of histamine base per 1,000 cc. physiologic saline solution)		4
0.5 cc. of ampule* containing 0.1 mg. of histamine base (0.05 mg. of histamine base)		1
0.3 cc. of ampule* containing 0.1 mg. of histamine base (0.03 mg. of histamine base)	Single intravenous dose	3
0.1 cc. of ampule* containing 0.1 mg. of histamine base (0.01 mg. of histamine base)		2
0.1 mg. of histamine base	Subcutaneous	1

* Contents of ampule given in text.

in mind that histamine is one of the most powerful drugs in the therapeutic armamentarium.

EXPERIMENTAL

We performed eighteen analyses of gastric content on eight subjects, each of whom had received a diagnosis of multiple sclerosis. Three subjects were subjected to three analyses; four subjects, to two analyses and one subject, to one analysis. The only drugs used in the study were histamine and benadryl. Histamine was administered subcutaneously and intravenously. Histamine diphosphate¹ (ampules containing 2.75 mg. of histamine diphosphate or 1.0

¹Abbott Laboratories, North Chicago, Illinois.

mg. of histamine base per 1 cc.) was used for continuous intravenous administration. One ampule in 250 cc. of physiologic saline solution represents a dilution of 1:250,000. For the administration of histamine in single doses, an ampule containing 0.275 mg. of histamine diphosphate or 0.1 mg. of histamine base in 1 cc. was used; amounts varying from 0.1 cc. to 0.5 cc. of this preparation were given. In table 1 the dilutions used are summarized.

The greatest amount of histamine was used in the first analyses, when a 1:250,000 dilution was administered by the intravenous drip method at a rate

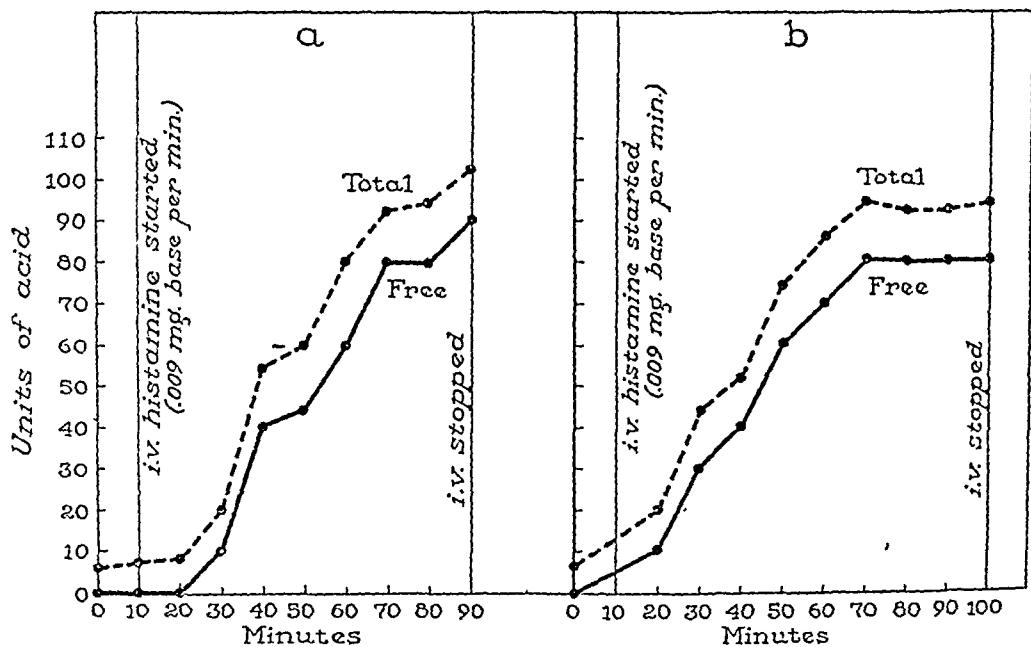


Fig. 1. The double histamine curve using histamine by the intravenous route. A 1:250,000 solution of histamine diphosphate was used on both occasions. The repetitive nature of the histamine curve is well demonstrated.

of 36 drops per minute (approximately 0.01 mg. per minute) for two hours. A total of approximately 1.3 mg. of histamine base therefore was given. This stands in striking contrast to the single intravenous dose of 0.01 mg. of histamine base used in the last analyses. It seems reasonable that a greater measure of control by means of benadryl might be attained with the smaller dose of histamine.

Benadryl was administered by the intravenous route in connection with all but six analyses. It was given by the oral route only on two occasions and by the combined oral and intramuscular routes on four occasions. The oral dose ranged from 400 mg. in fourteen hours preceding an analysis to 620 mg. in twenty-four hours preceding the test. On two occasions such oral doses were

supplemented by an intramuscular injection of 20 mg. as the fasting gastric specimen was taken. On all occasions except two, the dilution of benadryl

TABLE 2

Summary of data concerning the eight subjects employed in the eighteen analyses of gastric content

SUBJECT	YEARS AND SEX	DIAGNOSIS	NUM-BER OF ANAL-YSES	METHOD OF ADMINISTRATION		COMMENTS
				Histamine	Benadryl	
1	39 M	Multiple sclerosis	3	Continuous intravenous	Oral; oral and intramuscular	Suggestive evidence of inhibition by benadryl of histamine-induced rise. See fig. 2
2	32 F	Multiple sclerosis	2	Single dose intravenous	Intravenous	Suggestive evidence of inhibition by benadryl of histamine-induced rise. See fig. 3
3	26 F	Multiple sclerosis	2	Continuous intravenous	Intravenous	Suggestive evidence of inhibition by benadryl of histamine-induced rise. See fig. 4
4	31 F	Multiple sclerosis	2	Single dose intravenous	Intravenous	Suggestive evidence of inhibition by benadryl of histamine-induced rise. See fig. 5
5	34 M	Multiple sclerosis	1	Continuous intravenous	Intravenous	No response to histamine
6	33 F	Multiple sclerosis	3	Continuous intravenous	Oral; oral and intramuscular	No evidence of inhibition by benadryl of histamine-induced rise
7	20 F	Multiple sclerosis	3	Single dose intravenous; continuous intravenous	Intravenous	No evidence of inhibition by benadryl of histamine-induced rise
8	23 F	Multiple sclerosis	2	Continuous intravenous	Intravenous	Benadryl apparently provoked a rise of gastric acidity. See fig. 6

used was 60 mg. per 100 cc. of physiologic saline solution. In two early analyses a dilution of 40 mg. of benadryl per 100 cc. was used.

For the proper understanding of the gastric studies which shortly will be presented, it is essential to recall that the histamine-induced gastric curve is

capable of being repeated; that is, a subcutaneous injection of histamine on a second occasion will provoke a rise of gastric acidity almost identical with that

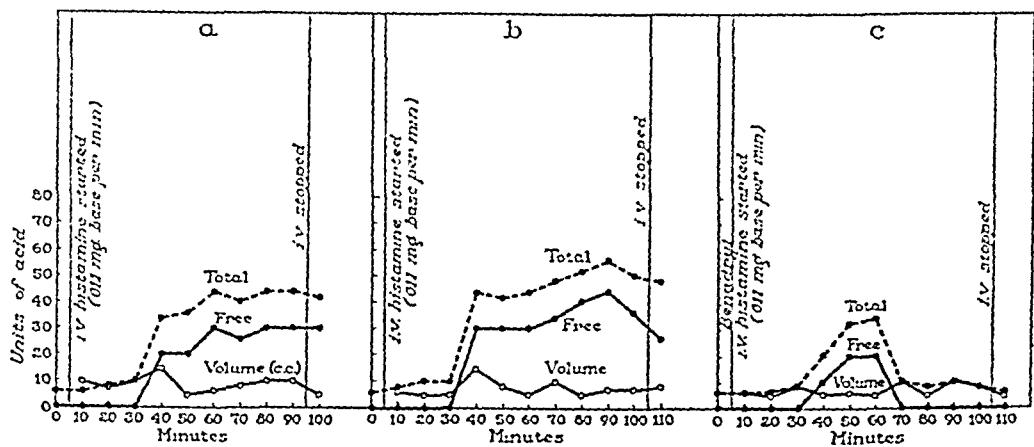


FIG. 2. Subject 1. A sequence of analyses made after administration of the following: *a*, Histamine alone; *b*, histamine intravenously and benadryl orally; in this set of observations, doses of benadryl and time before administration of histamine were as follows: 50 mg. and 14 hrs., 50 mg. and 11 hrs., 100 mg. and 9 hrs., 100 mg. and 6 hrs., and 100 mg. and 3 hrs.; *c*, histamine intravenously and benadryl orally and intramuscularly; in this set of observations, doses of benadryl and time before administration of histamine were as follows: 150 mg. and 48 to 24 hrs., 300 mg. and 24 to 9 hrs., 100 mg. and 9 hrs., 100 mg. and 6 hrs., 100 mg. and 3 hrs. The last administration of benadryl in this set of observations was of 20 mg. which was given intramuscularly immediately after the fasting specimen had been collected. When the parenteral route of administration of benadryl was utilized, some alteration of the curve seems to have occurred.

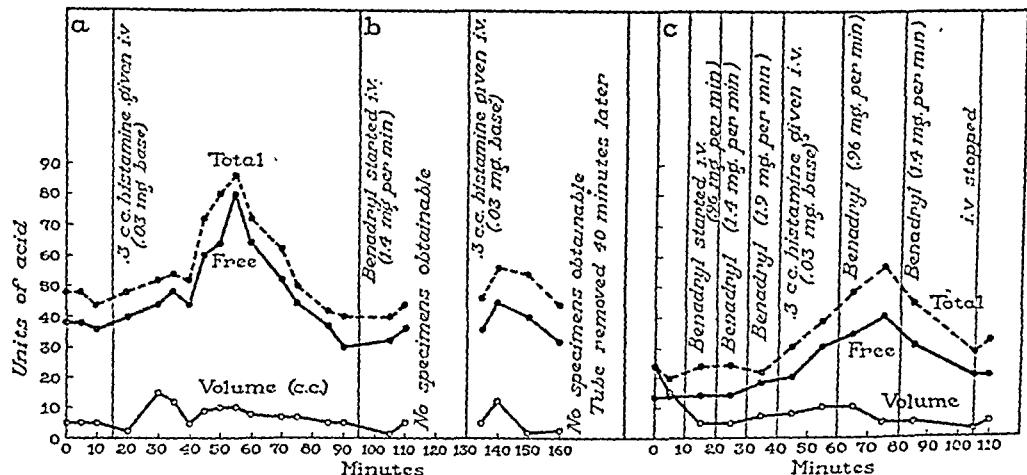


FIG. 3. Subject 2. The effect of intravenous administration of benadryl on gastric acidity provoked by intravenous administration of small doses of histamine. *a* and *b*. It became impossible to obtain a specimen of gastric secretion shortly after administration of benadryl was begun; therefore, on the following day the study was continued, establishing the conditions of *b*; *c*, the result of the analysis. Some alteration of the curve seems to have occurred.

provoked by a similar dose on a previous occasion. This has been described as the "double histamine curve" by Rivers, Osterberg and Vanzant (5). The

phenomenon of the double histamine curve also has been demonstrated by one of us (Horton) (6) (7) by the intravenous administration of histamine to twenty-seven patients with multiple sclerosis (fig. 1).

With this expectation of a similar curve on the second occasion that histamine is injected, it becomes most convenient to demonstrate the effect of various agents on gastric acidity by introducing such substances either before or during the administration of the second injection of histamine. Therefore, the first injection is a control of the second. We have proceeded according to this

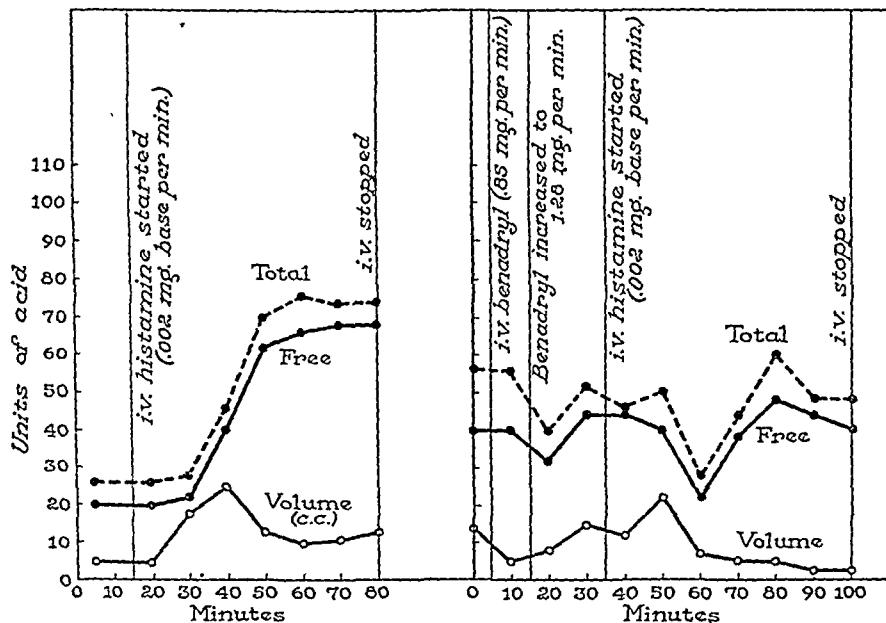


FIG. 4. Subject 3. The effect of intravenous administration of benadryl on gastric acidity provoked by constant intravenous administration of histamine. After administration of benadryl was begun, none of the factors charted—total acid, free acid, or total volume—ever significantly rose above the base line, even though histamine was given continuously.

general scheme and present the data recorded in table 2 and in figures 2 to 6.

It is not possible to make a significant statement concerning the effect of benadryl on the volume of gastric secretion because of the well-known difficulty of volumetric measurement of gastric secretion of human subjects. We do, however, have the impression that benadryl reduces the volume of gastric secretion and may increase its viscosity. On a certain occasion represented in figure 3 it became impossible to obtain a specimen of gastric content shortly after administration of benadryl had been begun. Similar difficulties in obtaining an adequate specimen were encountered frequently.

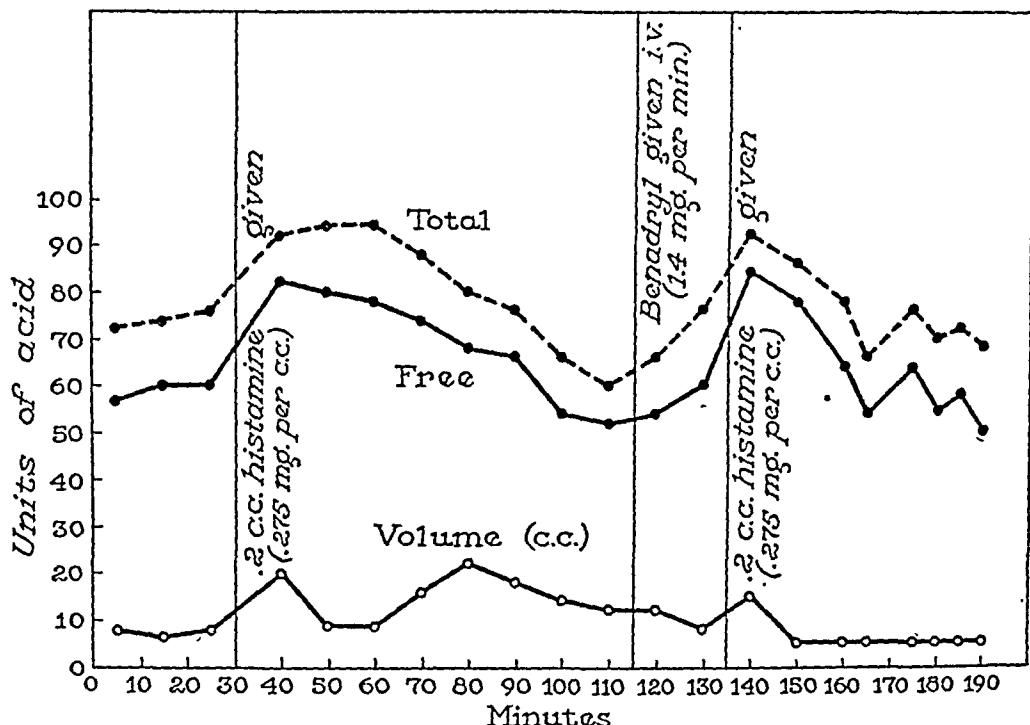


FIG. 5. Subject 4. An interesting variation of the possible inhibition of histamine-induced gastric acidity was seen in this case. After intravenous administration of benadryl, the histamine-induced rise of gastric acidity was maintained for only half as long as it had been maintained when histamine alone was given.

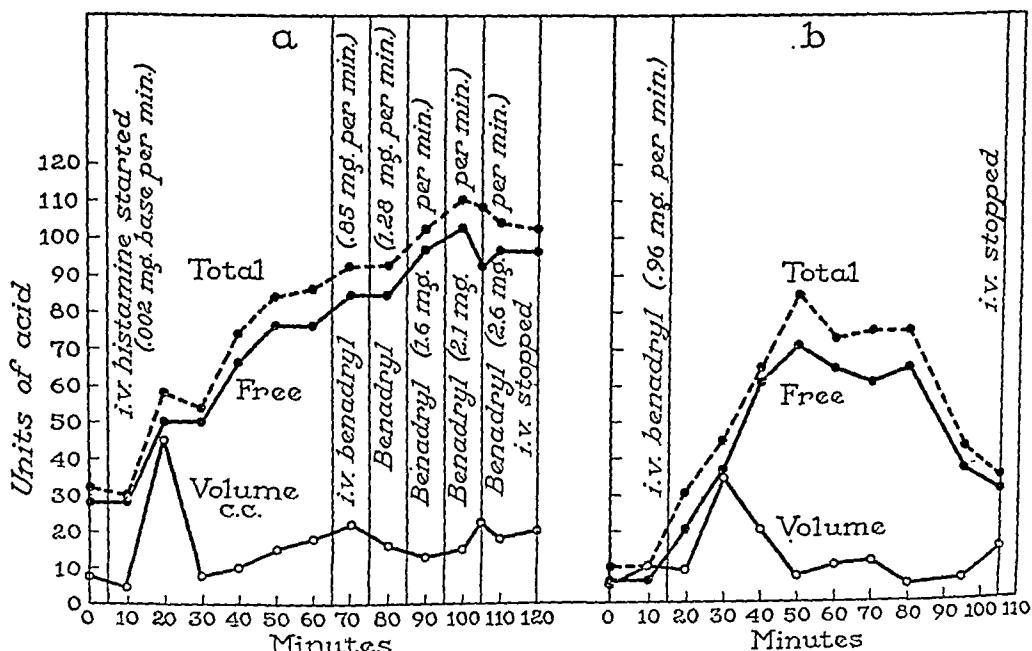


FIG. 6. Subject 8. *a*. In this instance benadryl was unable to check the rise of gastric acidity once it had begun. This was found to be true in all instances when benadryl was given *after* histamine. If suggestive inhibition of gastric acidity by benadryl was demonstrated, it was necessary to establish an effective concentration of benadryl by administering it by the parenteral route *before* administration of histamine; *b*, benadryl apparently provoked a rise of gastric acidity. The curve, however, was not sustained. This phenomenon is not explicable at this time.

SUMMARY

Our experience with the clinical use of benadryl in inhibiting the rise of histamine-induced gastric acidity in patients with multiple sclerosis is presented. The results to date have not been entirely consistent and do not readily lend themselves to analysis. There is, however, suggestive evidence that in some instances, the curve of gastric acidity is altered by this new antihistamine product. Our studies suggest that it is necessary to reduce the stimulating dose of histamine to a low order and to administer benadryl by the parenteral route to demonstrate this phenomenon. We wish to emphasize that we have investigated only the histamine-induced rise of gastric acidity in subjects with multiple sclerosis. We have not studied the effect of benadryl on normal gastric acidity or on the rise of gastric acidity induced by the test meal or any other agent. Particular attention is called to the fact that on one occasion benadryl seemed to provoke a rise of gastric acidity.

These preliminary analyses are presented because of the wide interest in the product under consideration and in all new antihistamine preparations. Further study is obviously necessary before any definite conclusions may be drawn.

ADDENDUM

For the sake of comparison with the published figures of Ivy and Javois (8) concerning the minimal amount of histamine base required to stimulate the gastric glands of dogs, we have calculated the following data:

In two subjects (weight 140 and 116 pounds [63.5 and 52.6 kg.]) given single intravenous injections of histamine, a rise of the gastric acid was obtained with an approximate dose of 0.0004 mg. of histamine base per kilogram of body weight.

In one subject (weight 125 pounds [56.7 kg.]) given histamine by the intravenous route continuously for a period of one hour, a rise of gastric acids was obtained and maintained with an approximate dose of 0.00003 mg. histamine base per kilogram of body weight per minute.

These approximate figures do not necessarily represent the minimal dose of histamine required to stimulate the gastric glands of man but are merely representative figures taken from our study.

REFERENCES

1. STAUB, ANNE-MARIE: Ann. Inst. Pasteur, 63: 400, 1939.
2. STAUB, ANNE-MARIE: Ann. Inst. Pasteur, 63: 485, 1939.
3. LOEW, E. R., AND CHICKERING, ORVILLE: Proc. Soc. Exper. Biol. & Med., 48: 65, 1941.
4. McELIN, T. W., AND HORTON, B. T.: Proc. Staff Meet., Mayo Clin., 20: 417, 1945; (Abstr.) Proc. Central Soc. Clin. Research, 18: 45, 1945.
5. RIVERS, A. B., OSTERBERG, A. E., AND VANZANT, F. R.: Am. J. Digest. Dis., 3: 12, 1936.
6. PETERS, G. A., AND HORTON, B. T.: Proc. Staff Meet., Mayo Clin. 15: 545, 1940.
7. HORTON, B. T.: Unpublished data.
8. IVY, A. C. AND JAVOIS, A. J.: Am. J. Physiol. 71: 604, 1925.

SEPARATION AND ASSAY OF SECRETIN AND CHOLECYSTOKININ¹

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INTRODUCTION

The success achieved by Hammersten and Agren, (1) as well as by Greengard and Ivy (2) in isolating crystalline secretin and testing it on animals and man, stimulated much interest as to the possibility of its use for diagnostic and therapeutic purposes. However, clinical application of secretin on a wide scale could not be carried out until a relatively cheap and abundant preparation² developed by Hammersten and Agren, was produced on a commercial scale.

The use of this preparation by Agren (3, 4, 5) in Sweden, and by Diamond (6-9) in this country, revealed many interesting clinical applications; namely in estimating pancreatic function in health and disease, as a test of gall bladder function, and in differentiating between various types of steatorrhreas.

Pancreotest was found to be a relatively impure preparation containing a considerable amount of inert material, although on injection in man it produced neither immediate reaction, nor sensitivity on repeated administration. It was obvious that the next and necessary step, if the use of secretin was to be popularized, was to make available an inexpensive preparation of pure secretin which could be standardized by weight instead of biologically.

This result could be achieved if the structure of the secretin molecule were determined and the substance synthesized. The tentative chemical analysis of pure secretin by Agren (10) and especially by Greengard and Ivy (2) indicated that the molecule of secretin, although of peculiar composition, finally might prove to be relatively simple. Indeed the findings of the latter investigators strongly suggested that the molecular weight of secretin base might be in the neighborhood of 250.

The purpose of this investigation was to produce pure secretin in the form of crystalline secretin-picrolonate in an amount large enough to determine the chemical structure of the secretin molecule. Unfortunately this work, which was begun in 1941, had to stop in 1942 and was not resumed until 1946. Accordingly, the observations detailed in this presentation are in the form of a preliminary report which may be of some assistance to workers in this field.

¹Aided by grants from the Eli Lilly Co., Indianapolis, and from the New York Foundation.

²Pancreotest, manufactured by the Astra Laboratories, Sodertalje, Sweden.

METHODS

The methods used for the isolation of secretin picrolonate, and incidentally of cholecystokinin, followed in all essential steps the procedure of Greengard and Ivy (2). However, only the first two feet of the hog's intestine, freshly obtained, instead of the first six feet were used for acid extraction. The first vasodilator free secretin preparation, precipitated by trichloracetic acid, was called S1. The second precipitate, S2, was obtained by further purification with aniline and methyl alcohol. The final product, crystalline secretin-picrolonate, was obtained by extraction of S2 with butyl alcohol, and precipitation of the aqueous residue with picrolonic acid. Evaporation of the carefully washed butyl alcohol extract contained the secretin-free cholecystokinin (CCK).

Secretin was assayed on the dog's pancreas *in situ* by the method of Ivy, Drewyer, and Lueth (11), slightly modified. The main pancreatic duct was intubated, and the accessory pancreatic duct, the pylorus, and the common bile duct ligated. The tube leading from the pancreatic duct emptied into a closed flask three-quarters full of a saturated sodium chloride solution, and a tube 30 cm. long led straight down from the flask to an electric drop recorder. The result was that the pancreatic juice was siphoned off by gentle suction, preventing obstruction, and that the electrodes of the drop recorder did not become clogged by the protein present in the pancreatic juice.

The assay of cholecystokinin on the dog's gall bladder was carried out at the same time as the secretin assay in a number of animals. In these animals the method of Ivy and Oldberg (12), as modified by Doubilet and Ivy (13), was used. The cystic duct was ligated, the common bile duct was allowed to drain freely to the outside, and a cannula with a side arm for adjusting the intravesical pressure to 7 cm. of bile was inserted into the fundus of the gall bladder. Kymograph tracings were recorded by means of a tambour. The arterial blood pressure was recorded kymographically on all dogs in which assays were done for secretin and cholecystokinin.

Cholecystokinin was also assayed on the isolated guinea pig's gall bladder, using the method of Jung and Greengard (14), as modified by Doubilet and Ivy (13). The intravesical pressure was adjusted to 4-5 cm. with Sollmann-Rademaeker's solution at the beginning of each experiment.

RESULTS

The S1 and S2 preparations obtained by the method of Greengard and Ivy (2) were found to be highly potent for both secretin and cholecystokinin, and free from vasodilator substances, as determined by blood pressure changes. These preparations were readily soluble in normal saline, especially if the dry powder was first triturated with one drop of concentrated HCl. The assay of

secretin-picrolonate was rendered difficult by its insolubility. The method used by Agren (11) and by Greengard and Ivy (2), of extracting the picrolonate acid by ether from an acidified suspension of the crystalline powder, was found to be tedious. Another handicap was the constant feeling that some portion of the very minute amounts used for assay might be lost in the above manipulations. A solvent relatively non-toxic was found in propylene glycol (15), in which the secretin-picrolonate dissolved readily when warmed for a minute in a water bath. One to two cubic centimeters of propylene glycol was used and the resulting solution then diluted five times with normal saline. Assays could then be carried out with ease. This solution of secretin-picrolonate in 20% propylene glycol was found to be quite stable. Solutions kept for 4 months in the ice-box were found to have an undiminished potency. Occasionally, a fine brownish precipitate would form at the bottom of the solution, but this dissolved readily on warming for a minute in a water bath.

The cholecystokinin obtained after evaporation of the butyl alcohol extracts, was quite small in amount and tended to be an amorphous, slightly gummy material, very difficult to handle. It was only partially soluble in water, but was found to be readily soluble in propylene glycol. This finding made its assay much more convenient.

Pancreotest was found to be readily soluble in hot saline.

The results of the assay of the various preparations of S1, S2, Pancreotest, and secretin-picrolonate, on the 13 dogs, are tabulated in table 1. As can be readily seen, the animals varied considerably in their reaction to secretin, some animals being quite refractory. This finding was also observed by Ivy (16) (17). In general, however, S1 was found to be twice as potent as Pancreotest, confirming the observations of Greengard and Stein (18). S2 was found, as a rule, to be twice as potent as S1.

Secretin-picrolonate was found to be extremely potent. In animals that were most sensitive to secretin, namely dogs 3, 4, 5, and 8, the threshold dose (Ivy Unit) was 0.050 mg. Dog 6 gave a threshold response to 0.066 mg., and dog 7 to 0.090 mg. On the other hand, many of the animals responded very poorly, 0.150-0.400 mg. being required to stimulate the pancreas to an increased secretion of 10 drops of pancreatic juice in 10 minutes.

Secretin forms only one fifth of the secretin-picrolonate molecule by weight, and since the threshold dose should be correlated with the body weight of the test animals, it was considered of interest to calculate the threshold dose (Ivy Unit) of secretin base per kilogram. This was found to be 0.00066 mg. or 0.66 gamma for the animals most sensitive to secretin (table 1, last column).

Various batches of secretin-picrolonate prepared at different times were found to be extremely consistent in their potency. For example, three different samples (a, b, c) tested on Dog 8 gave practically similar results.

TABLE 1

Relative potency of various secretin preparations as measured by the response of the dog's pancreas

DOG NO.	WT. KG.	S1		S2		PANCREOTEST		SECRETIN-PICROLONATE			IVY UNIT/ KG. FOR SECRETIN (1/5 SECRETIN- PICROLO- NATE) (GAMMA)
		Mg.	Pancreatic Juice (drops)	Mg.	Pancreatic Juice (drops)	Mg.	Pancreatic Juice (drops)	Mg.	Pancreatic Juice (drops)	Ivy unit Mg.	
1	14	1.0	13			1.5	4	1.0	40		
								0.5	15		
								0.3	11	0.300	4.3
2	14	1.5	16			1.5	6	0.2	3		
		1.0	14					0.4	10	0.400	5.7
3	14	1.0	20	1.0	55	1.0	8	1.0	210		
								0.25	52		0.66*
4	15	1.0	53	0.50	102			0.10	36		
		0.25	9	0.20	13			0.05	10	0.050	0.66
				0.10	6						
				0.15	10						
5	13	1.0	31			2.0	3	1.0	215		
											0.66*
6	13	1.0	22	0.5	17			0.2	45		
		0.5	9	0.3	11			0.066	9	0.066	1.0
7	14.5	1.0	15					1.0	100		
		0.8	9					0.1	9	0.090	1.4
8	15	0.5	27					a 0.10	24		
		0.25	9					0.075	18		
								0.05	10	0.050	0.66
								b 0.05	8		
								0.075	14		
								c 0.07	8		
9	12	1.0	30	0.5	22	1.0	9	0.1	1		
		0.5	9	0.25	4			0.2	17		
		0.25	1	0.375	10			0.15	7		
								0.175	10	0.175	3
10	13	1.0	50			1.0	8	0.2	15		
		0.5	9					0.15	8		
		0.75	28							0.175	2.7
11	12					1.0	9	1.0	83		
						5.0	85	0.6	35		
								0.3	12		
								0.25	10	0.250	4.6
								0.20	6		

TABLE 1—Concluded

DOG NO.	WT. KG.	S1		S2		PANCREOTEST		SECRETIN-PICROLONATE			IVY UNIT/ KG. FOR SECREtin (1/5 SECREtin- PICROLO- NATE) (GAMMA)
		Mg.	Pancreatic Juice (drops)	Mg.	Pancreatic Juice (drops)	Mg.	Pancreatic Juice (drops)	Mg.	Pancreatic Juice (drops)	Ivy unit Mg.	
12	10					0.80	9	1.00 0.20	114 11	0.200	4.0
13	12					2.0	43	1.00 0.25 0.15	142 22 10	0.150	2.5

* Approximate (Calculated).

TABLE 2
Assay of cholecystokinin on the isolated guinea pig gallbladder

NO.	SUBSTANCE	AMOUNT (MG.)	INITIAL PRESSURE (CM. WATER)	FINAL PRESSURE (CM. WATER)	RISE (CM. WATER)
1	S1 A	0.25	4	4.5	0.5
	S1 A	0.50	4.5	5.5	1.0
	S1 B	0.25	5.0	7.0	2.0
	S1 B	0.125	5.0	7.0	2.0
2	S1 C	0.50	4.0	8.0	4.0
3	S1 D	4.0	4.0	9.0	5.0
	S2 D	1.0	5.0	9.0	4.0
	S1 E	1.0	6.0	8.0	2.0
4	S1 E	0.5	5.0	10.0	5.0
	S1 D	0.5	5.0	9.0	4.0
	S1 E	0.1	6.0	7.0	1.0
	CCK* (saline)	0.25	7.0	8.0	1.0
5	S1 E	0.5	5.0	10.0	5.0
	S1 E	0.1	5.0	6.0	1.0
	CCK (saline)	0.5	6.0	9.0	3.0
6	S1 E	0.3	5.5	7.0	1.5
	S1 E	0.2	5.5	6.5	1.0
	S2 E	1.0	6.0	7.5	1.5
	CCK (saline)	0.5	5.0	9.0	4.0
	CCK (propyleneglycol)	0.1 (slow)	5.0	6.0	1.0
	CCK (propyleneglycol)	0.2 (slow)	5.0	7.5	1.5
	S1 E	0.1	6.0	7.0	1.0
7	S1 E	0.2	7.0	8.0	1.0
	S1 E	0.4	8.0	10.0	2.0
	CCK (propyleneglycol)	0.1	6.0	7.0	1.0
	CCK (propyleneglycol)	0.2	7.0	8.0	1.0

* CCK—Isolated Cholecystokinin obtained by evaporation of butyl alcohol extract in process of purifying Secretin.

The secretin-picrolonate salt was found to be very stable. Various samples had been kept in the ice-box in ordinary lightly corked tubes from 1942 to 1946. Retested in 1946 (dogs 11, 12, 13) using Pancreotest as a reference sample, the secretin-picrolonate was found to have retained its potency remarkably well. The animals used tended to be refractory, but comparative results were consistent as can be seen by comparing Dog 9 (tested in 1942) with Dog 12 (tested in 1946).

Control tests using propylene glycol (5 cc.) or picrolonic acid (25 mg.) dissolved in propylene glycol, had no effect either on the blood pressure or on the pancreas.

TABLE 3
Assay of cholecystokinin on the dog's gallbladder in situ

DOG NO.	SUBSTANCE	AMOUNT (MG.)	INITIAL PRESSURE (CM. WATER)	FINAL PRESSURE (CM. WATER)	RISE (CM. WATER)	PANCREATIC SECRETION
A	CCK (propyleneglycol)	2.5	7.0	8.0	1.0	0
B	Secretin-picrolonate	1.0	7.0	7.0	0	+++
	CCK (propylene-glycol)	1.0	7.0	?	++	0
	S1 13	1.0	7.0	?	+	+
5	S1	1.0	7.0	9.0	2.0	31
	CCK (propyleneglycol)	1.0	7.0	?	++	0
	Secretin-picrolonate	1.0	7.0	7.0	0	215
	Pancreotest	2.0	7.0	7.0	0	36
10	S1	1.0	7.0	9.0	2.0	50
	CCK propyleneglycol)	2.0	7.0	?	+	0
	Secretin-picrolonate	1.0	7.0	7.0	0	+++
	Pancreotest	1.0	7.0	7.0	0	8

Only preliminary work was done on the assay of cholecystokinin. The isolated guinea pig's gall bladder and the dog's gall bladder *in situ* were used. Certain difficulties in standardization were encountered. In spite of the fact that the intravesical pressure was carefully regulated (4-5 cm. of bile in guinea pigs, and 7.0 cm. in dogs) the guinea pig gall bladder was frequently found to be irritable, and the dog's gall bladder *in situ* relaxed very slowly after injection of cholecystokinin. In general 0.1 mg. S1 extract caused sufficient contraction of the guinea pig gall bladder to raise the pressure 1 cm. (table 2). Approximately similar results were obtained with cholecystokinin (secretin free) whether partially dissolved in saline, or completely dissolved in propylene glycol. The constant temperature bath in which the gall bladder was immersed had a capacity of 50 cc., so that the concentration of the various substances used was very low (one part in 500,000). Propylene glycol introduced into the bath by itself had no effect on the gall bladder, although it was noticed

that the viscus tended to contract more slowly when the cholecystokinin was introduced as a 20% propylene glycol solution.

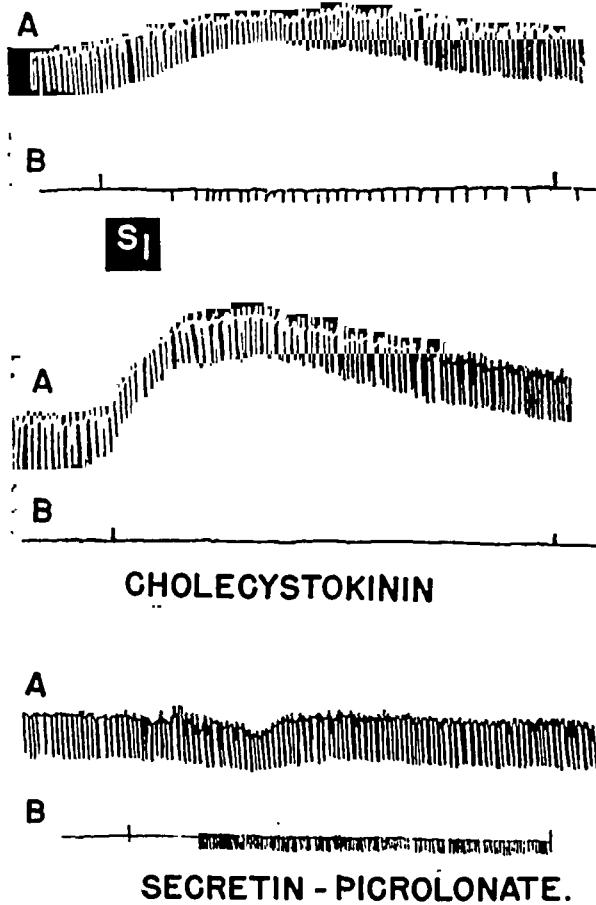


FIG. 1. SEPARATION OF SECRETIN AND CHOLECYSTOKININ.

Kymographic tracings of the contraction of the gall bladder (A) and the recording of drops of pancreatic juice (B) during a 10 minute period following the administration of 1 mg. each of S1, Cholecystokinin, and secretin-picrolonate. The S1 preparation caused both the gall bladder to contract and the pancreas to secrete 31 drops of pancreatic juice. The cholecystokinin caused active contraction of the gall bladder, but had no effect on the pancreas. The secretin-picrolonate did not affect the gall bladder, but stimulated the pancreas to secrete 215 drops of pancreatic juice. The blood pressure (not recorded here) taken simultaneously showed no change following the injection of these preparations.

In the dog (table 3) S1 had a CCK potency of 0.5 mg. (1 cm. bile rise from a base line of 7.0 cm. intravesical pressure). An insufficient number of experiments was done to standardize the assay of CCK dissolved in propylene glycol, but the CCK preparation showed only about twice the potency of the S1

preparation. Pancreatost was found to be quite free of cholecystokinin activity.

The best record of the separation of cholecystokinin from secretin and the relative increase in potency per mg. is represented in fig. 1 (Dog 5). One mg. of S1 caused the gall bladder to contract, and the pancreas to secrete 31 drops of pancreatic juice. The injection of 1 mg. CCK resulted in marked contraction of the gall bladder, but had no effect on the pancreas, which did not secrete in the resting phase. Injection of 1 mg. secretin-picrolonate obtained by purification of the same sample of S1 used in this experiment, caused the pancreas to secrete 215 drops of pancreatic juice in 10 minutes, but had no effect on the gall bladder.

DISCUSSION

The method of Greengard and Ivy for the production of crystalline secretin-picrolonate was found to be quite practical, although tedious and time consuming. Careful attention to details produced an apparently pure product of constant and high activity. The biological assay on the dog, however, demanded the use of a large number of animals, since many were refractory to secretin to a variable extent.

The observations of Greengard, Stein and Ivy (17), that the circulatory blood of the dog contained an enzyme, "secretinase", which inactivated secretin, and also an enzyme which inactivated cholecystokinin (19), are of great importance. The presence of such enzymes may account very well for the differences in sensitivity to secretin displayed by different dogs. If such is the case, any substance inhibiting the action of these enzymes should increase the activity of secretin and cholecystokinin.

It is known that choline esterase is inhibited by the action of certain drugs, such as eserine and prostignin (20), thiamine (21), methylene blue (22), and vitamin K (menadione) (23). Since powerful proteases such as pepsin or trypsin do not destroy secretin (17), it was thought that the "secretinase" found by Greengard et al. might be similar to choline esterase. If such were the case, some insight into the structure of secretin might be obtained. Accordingly Vitamin K was added to a sample of blood mixed with secretin, and the mixture incubated. As can be seen from table 4, vitamin K definitely inhibited the action of secretinase. When 4 mg. of vitamin K were injected intravenously, the action of secretin was enhanced by 50%. Vitamin K itself did not stimulate the pancreas.

This is a preliminary experiment, but it suggests certain possibilities. Secretinase may have an action similar to choline esterase itself. In the second place, by the use of similar inhibitors, the action of secretinase might be overcome during the biological assay of secretin and a more consistent and basic test

might be evolved. Thirdly, more insight might be gained into the chemical structure of secretin.

The production of crystalline secretin-picrolonate from the S1 preparation was a fairly efficient process, since about 50% of the original activity was recovered in the picrolonate salt. The stability of this salt, and its solubility in propylene glycol, suggests its use for pancreatic function tests in humans. However, before that can be done, the possibility of sensitizing humans to picrolonic acid must be excluded.

The method used for the purification of secretin was completely inefficient for isolating cholecystokinin, since the end product recovered from the butyl alcohol extraction contained only a minute amount of cholecystokinin, mixed

TABLE 4
Effect of synthetic vitamin K on secretinase*

EXPERIMENT	INCUBATED AT 37°C (MINUTES)	PANCREATIC JUICE (DROPS)
1. 2.0 mg. Pancreatost (0.5 cc.)	0	43
2. 2.0 mg. Pancreatost (0.5 cc.) + 4.5 cc. whole blood + 1.0 cc. normal saline	30	31
3. 2.0 mg. Pancreatost (0.5) + 4.5 cc. whole blood + 1.0 mg. vit. K. (1.0 cc.)	30	44
4. 0.5 cc. normal saline + 4.5 cc. whole blood + 1.0 mg. vit. K. (1.0 cc.)	30	0
5. 2.0 mg. vit. K. intravenously; followed by 2.0 mg. Pancreatost; followed in 3 minutes by 2.0 mg. vit. K.		61

* Synkanin (Parke-Davis)—4-amino-2 methyl-1-naphthol as hydrochloride.

with a considerable amount of inert material. It was only slightly more potent than the S1 preparation, which with all its impurities, was apparently more potent than Agren's cholecystokinin (24). Much work remains to be done before cholecystokinin can be purified as highly as secretin. However, if the molecular structure of secretin should be determined, it might help to unlock the secret of the chemical nature not only of cholecystokinin, but also of the other intestinal hormones.

CONCLUSIONS

1. A highly purified crystalline secretin-picrolonate was consistently produced from hog's small intestine by the method of Greengard and Ivy.
2. Secretin and cholecystokinin could be readily separated by this method.
3. The Ivy Unit potency of the secretin-picrolonate was about 0.050 mg. for

the dogs most sensitive to secretin. This potency calculated as secretin base per kilogram body weight was 0.00066 mg.

4. The action of secretinase is inhibited by vitamin K (menadione).

BIBLIOGRAPHY

1. HAMMARSTEN, E., AGREN, G., HAMMARSTEN, H., AND WILANDER, O.: Versuche zur Reinigung von Sekretin. *V. Biochem. Z.*, **264**: 275, 1933.
2. GREENGARD, H., AND IVY, A. C.: The Isolation of Secretin. *Amer. J. Physiol.*, **124**, 427; 1938.
3. AGREN, G., AND LAGERLOF, H.: The Pancreatic Secretion in Man after Intravenous Administration of Secretin. *Acta Med. Scand.*, **90**: 1, 1936.
4. AGREN, G., LAGERLOF, H., AND BERGLUND, H.: The Secretin Test of Pancreatic Function in the Diagnosis of Pancreatic Disease. *Acta Med. Scand.*, **90**: 224, 1936.
5. AGREN, G. AND LAGERLOF, H.: The Biliary Response in the Secretin Test. *Acta Med. Scand.*, **92**: 359, 1937.
6. DIAMOND, J. S., SIEGEL, S. A., GALL, M. B., AND KARLEN, S.: The Use of Secretin as a Clinical Test of Pancreatic Function. *Amer. J. Digest. Dis.*, **6**: 366, 1939.
7. DIAMOND, J. S., SIEGEL, S. A., AND MYERSON, S.: The Biliary Pigment Curve during the Secretin Test. *Amer. J. Digest. Dis.*, **7**: 133, 1940.
8. DIAMOND, J. S., AND SIEGEL, S. A.: The Secretin Test in the Diagnosis of Pancreatic Diseases, with a Report of One Hundred Thirty Tests. *Amer. J. Digest. Dis.*, **7**: 435, 1940.
9. DIAMOND, J. S., SIEGEL, S. A., AND MYERSON, S.: The Secretin Test as an Aid in the Differential Diagnosis of the Steatorrhreas, with a report of Fourteen Cases. *Rev. Gastroenterol.*, **7**: 429, 1940.
10. AGREN, G.: Ueber die Pharmakodynamischen Wirkungen und Chemischen Eigenschaften des Secretins. *Skand. Arch. Physiol.*, **70**: 10, 1934.
11. IVY, A. C., KLOSTER, G., DREWYER, G. E., AND LUETH, H. C.: The Preparation of a Secretin Concentrate. *Amer. J. Physiol.*, **95**: 35, 1930.
12. IVY, A. C., AND OLDBERG, E.: A Hormone Mechanism for Gall Bladder Concentration and Evacuation. *Amer. J. Physiol.*, **86**: 599, 1928.
13. DOUBILET, H., AND IVY, A. C.: The Response of the Smooth Muscle of the Gall Bladder at Various Intravesical Pressures to Cholecystokinin. *Amer. J. Physiol.*, **124**: 379, 1938.
14. JUNG, F. T., AND GREENGARD, H.: Response of the Isolated Gall Bladder to Cholecystokinin. *Amer. J. Physiol.*, **103**: 275, 1933.
15. SEIDENFELD, M. A. AND HANZLIK, P. J.: The General Properties, Action, and Toxicity of Propylene Glycol. *J. Pharm. and Exp. Therap.*, **44**: 109, 1932.
16. GREENGARD, H., STEIN, I. F. AND IVY, A. C.: Certain Quantitative Aspects of Pancreatic Response to Secretin. *Amer. J. Physiol.* **132**: 305, 1941.
17. GREENGARD, H., STEIN, I. F., AND IVY, A. C.: Secretinase in Blood Serum. *Amer. J. Physiol.* **133**: 121, 1941.
18. GREENGARD, H., AND STEIN, I. F.: Assay of Secretin. *Proc. Soc. Exp. Biol. and Med.*, **46**: 149, 1941.
19. GREENGARD, H., STEIN, I. F., AND IVY, A. C.: The Enzymatic Inactivation of Cholecystokinin by Blood Serum. *Amer. J. Physiol.*, **134**: 733, 1941.
20. ROEFKE, M. H.: Study of Cholinesterase. *J. Pharm. and Exp. Therap.*, **59**: 264, 1937.
21. GLICK, D.: Inhibition of Choline Esterase by Thiamine (Vitamin B). *J. Pharm. and Exp. Therap.*, **65**: 389, 1939.
22. RENTZ, E.: Methylenblau und Cholinesterase. *Arch. f. exper. Path. u. Pharmakol.*, **196**: 148, 1940.
23. TORDA, C., AND WOLFF, HAROLD, G.: Effect of Vitamin K (Menadione) on Choline Esterase Activity, Acetyl-choline Synthesis, and Striated Muscle. *Proc. Soc. Exper. Biol. and Med.*, **57**: 236, 1944.
24. AGREN, G.: On the Preparation of Cholecystokinin. *Scand. Arch. Physiol.*, **81**: 234, 1939.

Section on
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CLINICAL PATHOLOGICAL CONFERENCE

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Presentation of Case (B-13655): The patient, a fifty-three year old white man, was admitted to Duke Hospital, complaining of diarrhea, loss of weight, marked weakness and dyspnea on exertion over a period of several months. He seems to have been in reasonably good health until two years ago, at which time he developed a mild diarrhea without blood or pus. He noted that the stools were quite foul. His diarrhea has been intermittent since the onset; at times having six to eight stools per day, at times clearing up almost entirely. During the past few months, however, his diarrhea has increased and occasionally he has been able to recognize in the stool particles of food recently eaten. During this time he has lost thirty pounds in weight and has developed marked swelling of the feet and legs, shortness of breath, and extreme weakness. His diet has consisted largely of milk, eggs, liver, and green vegetables. There has been some nausea and vomiting from time to time but no abdominal pain.

His past history is of interest in that he had a typical picture of peptic ulcer about fifteen years ago. He was operated upon for perforation and also had a gastroenterostomy. After operation he followed a modified Sippy regime without recurrence of symptoms.

Physical examination: An emaciated white man, who was so weak that he was unable to sit up in bed, with marked edema of the extremities. His skin was dry and loose and showed evidence of recent weight loss. The mucous membranes were pale. The tongue was entirely normal, there being no evidence of papillary atrophy or cheilosis. The heart and lungs were clear. Blood pressure 80/40. The abdomen was slightly distended and tympanitic; there was an upper midline incision, well healed; no masses or tenderness; no peristaltic waves could be seen. There was a 4+ pitting edema of the feet and legs. Rectal examination was negative. Proctoscopic examination was likewise negative.

Accessory clinical findings: There was a macrocytic anemia, his hemoglobin being 75%. RBC 3,100,000. Color index 1.2; urine negative. Stool was

foul; there was no blood and a few undigested particles of food were seen; benzidine was repeatedly negative. NPN 34 mg.%. Total proteins were low (4.1 gm.%) with a low albumin 1.4 gm.%) and an inverted A/G ratio (0.51). Globulin 2.7. Serum calcium 6.3 mg.%. Gastric analysis showed no free acid; stool fat 67%.

Course in hospital: Every effort was made to build him up by a high protein diet, supplemented by large doses of vitamins. He was given repeated transfusions of plasma and whole blood and intravenous fluid. His diarrhea continued unabated. On the nineteenth hospital day, exploratory laparotomy was performed. The patient reacted poorly and died in circulatory collapse on the second post-operative day.

Differential diagnosis: *Dr. Ruffin:* This man presents an interesting diagnostic problem. Such diseases as chronic idiopathic ulcerative colitis, amoebic dysentery, carcinoma of the colon, intestinal polyposis, tuberculosis of the intestine, and regional ileitis all have to be considered. However, a negative proctoscopic study and the persistently negative benzidine of the stool make it improbable that he had an ulcerating lesion of the colon, and I doubt that he had any of the above mentioned conditions. An important group to consider would be the deficiency diseases. His diet was entirely adequate and he has never had a sore mouth or tongue which renders it unlikely that his diarrhea was on the basis of a vitamin deficiency. He could well have had sprue and certainly had the sprue syndrome; namely, a fatty diarrhea (stool fat 67%), a macrocytic anemia, and marked weight loss. Whipple's disease, or lipophagic dystrophy, is a definite possibility. His edema, of course, is explained on the basis of his low serum proteins and an inverted A/G ratio. Obviously he was not absorbing his food which makes one feel that he had either an extensive disease of the intestine or that he had a shunt, as suggested by the presence of food particles in the stool. Without x-ray studies a more accurate diagnosis is not possible.

Could we see the x-rays?

Dr. Baylin: Barium studies were of unusual interest. The stomach showed some hypertrophy of the folds and there was a notch in the superior portion of the duodenal bulb, indicative of an old ulcer. The barium entered the duodenum readily but there was no evidence of any gastroenterostomy opening. The duodenum was greatly dilated and there was a marked delay for thirty minutes in the region of the duodenojejunal junction. The barium finally passed into an extremely dilated loop of jejunum high in the left upper quadrant. At the end of one hour the barium was still located in loops of the jejunum with no evidence of any barium entering the colon. The twenty-four hour film showed the intestinal tract practically empty. There was no evidence of the presence of a gastrocolic fistula from this examination. However, when studied by

barium enema, the barium appeared to enter from the colon to the jejunum and then into the stomach. The obvious explanation is that there exists an enterocolic fistula and that the barium enters the stomach through a post-operative stoma, which was occluded functionally when oral barium studies were done. The liver appears to be greatly enlarged and a plain film of the abdomen shows a few opacities in the left kidney region, but we cannot be certain that they actually represent kidney stones. There is no evidence of pancreatic calculi.

Discussion: Dr. Ruffin: In view of the x-ray findings, this man obviously had a gastroenterocolic fistula. The lesson to be learned here is that the diagnosis could have been missed had we depended entirely upon barium by mouth and omitted the barium enema. It is important to bear in mind that any patient having a history of ulcer, particularly one who has had a gastroenterostomy, and develops a diarrhea with recognizable particles of food in the stool, should always be suspected of having a gastroenterocolic fistula. The tragedy of this case was failure to recognize the condition in time and the fatal outcome was due to his general debility and inability to withstand operative procedure.

Clinical diagnosis: Gastroenterocolic fistula with emaciation.

Pathological discussion: Dr. Margolis: At operation a communication was found between the stomach, jejunum, and transverse colon. This had been produced by the occurrence of an ulcer at the right border of the old posterior gastrojejunostomy opening, and its perforation into the overlying adherent transverse colon. The duodenum and jejunum were dilated, but no anatomical reason for this could be demonstrated. The operative procedure consisted of a closure of the fistula, leaving the gastrojejunostomy opening as it was originally.

At autopsy a large embolus was found occluding the left pulmonary artery. A few smaller emboli were seen in small branches of the right pulmonary artery. These emboli were probably the immediate cause of death of the patient. Their source was not demonstrated.

No hemorrhages had occurred from the operative site. The dilatation of the duodenum and jejunum was still present, but this appeared to be the result of lack of muscular tone, since no obstruction could be demonstrated. A careful examination of the stomach and duodenum failed to disclose any areas of scarring suggestive of an old healed ulcer, and there was no evidence of any operative procedures other than those related to the gastroenterostomy. The most striking general feature presented at autopsy was the extreme emaciation. Another conspicuous finding was the presence of a moderate enlargement and an extreme degree of fatty change in the liver. This accumulation of fat resembled the changes produced in experimental animals with deficient diets.

Anatomical diagnosis: Gastrojejunocolic fistula, with operative closure, emaciation, fatty change of liver, massive pulmonary embolus.

CLINICAL PATHOLOGICAL CONFERENCE

A. J. ATKINSON, M.S., M.D.

Passavant Memorial Hospital, Chicago, Ill.

Presentation of the case (86148): A white man, age 53 years, entered the hospital complaining of a hacking cough, loss of appetite and fatigue. He had been in fairly good health until two weeks previous to admission. He then developed an upper respiratory infection which was followed by a cough and gradual increase in size of the abdomen. In two weeks his weight increased eight pounds. The cough and abdominal distention interfered with his sleep. A history was obtained of infrequent bouts for several years of "upset stomach" relieved by antacids. He had been a heavy drinker, but for many years had used no alcohol.

Physical examination revealed a well-nourished man with no acute discomfort. The right half of the chest showed limited expansion both on observation and palpation. At the right base posteriorly there was dullness on percussion and failure of voice-sound transmission. The left diaphragm was high. The abdomen was distended and a fluid wave was elicited. The liver, palpable 4 cm. below the mid-costal margin, was hard and nodular with no tenderness. The prostate was slightly enlarged and of normal consistency; the median sulcus was present.

Red blood cells 4,410,000, Hgb. 13 gm., white cell count 4,100 with 86 per cent neutrophils. Blood Wassermann negative. Serum phosphorus 3.49 mg., alkaline phosphatase 2.77 units. The serum protein was 4.6 gm. with 3.30 gm. of albumin and 1.3 gm. of globulin. The sedimentation rate 13 mm. per hour (Wintrobe), hematocrit 51 %, and the mean corpuscular volume 1.16 cu. micra. Icterus index 10 units. Prothrombin time 19.0 seconds (normal 17.6). A bromsulphalein test revealed 50 per cent retention of the dye in one hour. Urine and stool normal.

Clinical course: A chest film showed evidence of considerable fluid in the right pleural cavity. Roentgenologic examination revealed ascites but no abnormality of the digestive tube.

On the fifteenth day paracentesis yielded 6,000 cc. of red-tinged ascitic fluid which contained 332 cells per cu. mm. No organisms were found on direct smear. There was no growth after 72 hours. The total protein of the ascitic fluid was 2.66 gm. No tumor cells were found in sections of the sediment obtained after centrifuging.

On the twenty-fourth day a second paracentesis was performed and 6,000 cc. of fluid removed. Again no tumor cells were found on paraffin section. The

cells in the sediment were chiefly white blood cells with mononuclear cells predominating.

On the thirtieth day, dyspnea became marked. The right thorax was dull to percussion and breath sounds were absent. A thoracentesis was performed and 4,000 cc. of clear, yellow fluid obtained. The fluid contained 53,200 cells per cu. mm., mostly red blood cells. No bacteria were seen on direct smear and cultures were negative after 72 hours incubation. No tumor cells were found on paraffin section.

Following the thoracentesis a roentgenogram revealed fluid to the fourth rib anteriorly on the right side of the chest; there now was evidence of infiltration with consolidation, and possible cavitation, in the right upper lobe. The left lung was clear. Sputum examination showed no acid-fast bacilli.

A third abdominal paracentesis was performed on the thirty-fourth day and 8,500 cc. of fluid removed. It was found that the liver had increased in size and the spleen was palpable.

The condition of the patient became progressively worse and he died on the fifty-third hospital day.

Differential diagnosis: Generalized enlargement of the liver is most frequently due to cirrhosis, decompensated heart disease, an obstructed liver with jaundice, carcinoma, syphilis, malaria, or Banti's disease.

In this patient a history of chronic alcoholism makes necessary the consideration of *cirrhosis*. His liver was large, hard, and uneven and the spleen was palpable three weeks before death. In cirrhosis the spleen is often palpable. Hematemesis and melena usually occur at some period due to engorgement of the veins of the stomach and esophagus. In our patient there was no hematemesis, melena, or dilatation of the veins around the umbilicus, and no evidence of dilated esophageal veins was seen on fluoroscopic examination with barium. Nor were there dilated hemorrhoidal veins or spider telangiectases. Ascites occurs, of course, in many cases of cirrhosis. The lung findings in this patient could not be explained by cirrhosis. The blood findings on admission and for the first four weeks were also not consistent with those usually seen in cirrhosis, where there is usually a macrocytic anemia, a decreased serum protein with an elevated serum globulin, and a reduced prothrombin time. The infrequent bouts of stomach upsets, relieved by antacids, could be explained by chronic gastritis caused by alcoholic excess.

Cardiac decompensation can be quickly ruled out because there is an absence of the usual signs and symptoms of decompensation and edema of the legs is absent despite the presence of marked ascites.

Syphilis of the liver is uncommon at the bedside and rarely causes ascites or produces general symptoms. With syphilis, the liver is not greatly enlarged

unless lardaceous disease is associated. In this patient the Wassermann reaction was negative and there was no history of syphilis.

The lardaceous liver may be very large. It is very smooth and firm, and the edge is sharp and hard. An enlarged spleen may also be present, and evidence of kidney or intestinal disease may be seen. In this patient, there was no chronic suppuration nor syphilis to cause lardaceous disease and this condition would not account for the rapid lung changes.

Splenic anemia (Banti's disease) is accompanied by secondary anemia, leukopenia, and a tendency to bleed. Enlargement of the spleen usually antedates that of the liver and the patient frequently vomits blood long before the stage of cirrhosis of the liver is reached. Moreover, the anemia is quite severe.

In hydatid tumors the liver is smooth and regular; usually there are only one or two cysts. Eosinophilia may be present and the spleen may be enlarged. Progression is very slow and the general health is little impaired.

Carcinoma is the most common tumor of the liver. The edge is hard, frequently irregular and apt to become nodular as in our case. Sometimes the nodules feel umbilicated. Although there generally are symptoms of primary malignant disease elsewhere, not infrequently these are not present until the hepatic carcinoma is well advanced. Ascites and jaundice are the most important findings. Irregular fever is common. During the illness of our patient a temperature rise, between 100 and 102 F., was present only on 12 of 53 days. The changes in his lungs could be accounted for by metastatic carcinoma.

Primary sarcoma is very rare and clinically cannot be distinguished from carcinoma. However, the spleen is rarely if ever enlarged in sarcoma.

Malignant lymphoma, including lymphosarcoma, giant follicular lymphoma, lymphatic leukemia, and Hodgkin's disease should be considered. Lymphatic leukemia is readily recognized by the blood picture and can be excluded in our patient, in whom, moreover, no lymphadenopathy was detected. In any lymphoma the signs and symptoms result from space occupying lesions pressing on important structures. In Hodgkin's disease the lymph nodes are affected in the following order of frequency: cervical, submaxillary, clavicular, axillary tracheobronchial, mediastinal, and retroperitoneal. About 60 per cent of the cases start in the peripheral nodes, 30 percent in the thoracic nodes and 10 percent in the abdominal nodes and spleen. Early there may be lymphocytosis and later a leukopenia with a neutrophilia. The Pel-Ebstein type of fever is usually present when the abdominal viscera are affected. In our patient the fever might be considered to be of this type. The diagnosis of any of the malignant lymphomas, excluding lymphatic leukemia, is admittedly dependent on a histological study of an excised node, and with no lymphadenopathy in this case, there, there was no indication for a biopsy study.

Clinical diagnosis:

1. Hepatomegaly due to neoplasm
2. Splenomegaly
3. Ascites
4. Pleural effusion

Anatomical diagnosis:

1. Hodgkin's disease demonstrated microscopically in the: lymph nodes, prostate, kidney, periadrenal tissue, lung, pancreas, liver, and spleen
2. Hepatomegaly
3. Splenomegaly
4. Ascites—8,000 cc.
5. Pleural effusion—4,000 cc. (right)
6. Hepatic passive congestion—marked
7. Pulmonary congestion—slight (left)
8. Pulmonary atelectasis—right lower lobe.

This patient had a very diffuse type of Hodgkin's disease which had spread to nearly every organ in the body.

The liver was enlarged, weighing 2,690 grams, its surface smooth, the edges rounded and the consistency firm. It had what appeared to be several small accessory lobes. These lobes probably account for the clinical findings of a nodular liver on palpation. On cut section it had a nutmeg-like appearance. Microscopically there were marked peribiliary collections of Hodgkin's granulomatous tissue; moderate fatty infiltration, and a diffuse fibrous increase in some areas was noted.

Microscopically, lymph nodes from the abdomen and mediastinum presented the following picture: all normal structure was lost. There was a diffuse growth of endothelial cells; some were rounded, some elongated, and some polygonal ranging from 10-16 micra. There were some larger cells, to 40 micra, occasionally multinucleated; these had dense opaque, carmine-colored cytoplasm. The nuclei were large, reticulated, and showed large nucleoli. A few scattered eosinophiles and lymphocytes were seen. The cells infiltrated through the node capsule and were found diffusely in fat and other adjacent tissue.

Comment: Pleural effusion is a frequent complication of Hodgkin's granuloma. It is dependent upon involvement of the mediastinal nodes or granulomatous lesions of the pleura. This patient had extensive involvement of the mediastinal nodes, and the right pleura was diffusely infiltrated by Hodgkin's nodules.

Ascites is not common in Hodgkin's disease, occurring only in about one-sixth of the cases showing hepatomegaly. If it does occur, it is usually a terminal complication. This patient lived about ten weeks after the appearance of ascites.

At necropsy a few hard, shotty glands were felt in the right supraclavicular and right inguinal regions. These were missed on physical examination and accordingly no biopsy was made.

CLINICAL-PATHOLOGICAL CONFERENCE*

H. M. POLLARD, M.D.

University Hospital, Ann Arbor, Michigan.

Presentation of case: The patient, sixty-two year old janitor, experienced sudden, sharp, lower abdominal pain localized to the left of the suprapubic region. This pain was not of sufficient intensity to prevent his driving home, a distance of eighteen miles, to consult his physician.

On admission to the hospital two weeks later, the patient was complaining of paroxysms of cramps starting in the lower abdomen and becoming generalized. There was no associated nausea, vomiting, shock or fever. There was no history of recent or remote gastro-intestinal disturbance, and at no time had the patient ever vomited blood or bile. The stools were normal in consistency and color.

Aside from measles, mumps, chickenpox and scarlet fever in childhood, the patient had always been in good general health. He had an asymptomatic left femoral hernia for twenty-five years.

Physical examination revealed an acutely ill, emaciated, white male. The temperature was 99.6°, pulse 100, respirations 20, and blood pressure 120/70.

The chest was barrel-shaped; respiratory excursions were not limited. Fremitus was present throughout. The percussion note was decreased in intensity in the intrascapular region just to the right of the spine. In the same area, spoken voice sounds were diminished, and a long respiratory wheeze was audible which did not clear after expectoration.

The abdomen was distended symmetrically. It was quiet on auscultation, and on percussion it was tympanitic without shifting dulness. The liver was palpable three fingerbreadths below the right costal margin and a vague mass was palpable in the left upper quadrant. The size of this mass could not be ascertained due to abdominal distention. In the left inguinal region there was a mass of approximately two centimeters, which was firm and apparently fixed to the surrounding tissue. It was reducible and no impulse was elicited on coughing.

The routine blood Kahn was negative. The urine revealed a faint trace of albumin in every specimen examined and one or two red blood cells with five to twenty white blood cells per field and an occasional specimen with granular casts was seen. On admission hemoglobin was sixty-eight per cent; red blood cell count 3,800,000; white blood cell count 13,700; with a differential of eighty-four per cent polys, thirteen lymphocytes, and three monocytes. Subsequent examination revealed a persistent fall in the hemoglobin to twenty-five per cent, rising to fifty-six per cent, with daily transfusions. A check

* Presented before Refresher Course in Internal Medicine, University Hospital, Ann Arbor, Michigan.

hemogram revealed red blood cells 3,000,000; hemoglobin fifty-six per cent; white blood cells 8,000; differential eighty-five per cent polys, one eosinophil, twelve lymphocytes and two monocytes. An electrocardiogram showed no definite evidence of myocardial infarction. Serum bilirubin was 0.1 milligrams; total serum protein 5.04 per cent; plasma cevitamic acid 0.5 per cent; sodium chloride 514 milligrams per cent; plasma CO₂-combining power, 51 volumes per cent. Acid phosphatase was 4.5 units. Three-day sputum concentrate gave a pyogenic culture showing Streptococcus hemolyticus, Streptococcus viridans and a non-hemolytic Streptococcus.

Admission scout film of abdomen had revealed no evidence of intestinal obstruction. Roentgen ray examination of the upper gastro-intestinal tract was negative, with some delay in passage of the barium to the small bowel. Homogeneous increased density over the upper abdomen was mentioned. A barium enema failed to reveal extrinsic or intrinsic lesions. A roentgenogram of the chest revealed a small oval nodule of the right mid-lung, and elevation of the left leaf of the diaphragm.

A conservative regime of treatment was undertaken. The abdomen was decompressed by Wangensteen suction. After decompression it was obvious ascites was present, and paracentesis yielded 3,000 cc. of fluid. Examination of this fluid showed no neoplastic cells and culture was negative. The patient vomited on several occasions; the vomitus was coffee-ground in character. He also had numerous stools, some containing bright red blood and some tarry. His course was downhill in spite of all conservative measures and respirations ceased four weeks after admission.

Differential Diagnosis: Dr. H. Marvin Pollard: Analyzing the present illness, first of all, it seems to me that there are several diagnoses which are suggested, and a few statements which are probably misleading. You will note that while the lower abdominal pain was crampy in nature, it did not produce nausea and vomiting, and it began in the left lower quadrant. Also, there was no radiation into the left groin or down into the leg. There is no statement about urinary symptoms, but the diagnosis I would consider at the outset would be, 1) carcinoma of the left colon with an onset of partial obstruction bearing some relation to the automobile trip, 2) some disturbance in the left kidney, such as a hydronephrosis with possible a kink in the ureter, 3) a dissecting aneurysm, 4) an incarcerated hernia, even though this seems very unlikely.

The past history is not very helpful.

The physical examination presents several illuminating points, some of which are paradoxical. Apparently the patient was acutely ill, but even so his temperature was only 99.6°, and he was emaciated. This emaciation seems very significant, and although not supported by the history, suggests that

he had a chronic debilitating disease that had caused weight loss. He was apparently not in shock, at least to any significant degree, since his blood pressure was 120/70. The physical findings in the chest, of dulness in the interscapular area and at the same time *diminished* spoken voice sounds in the same area is an inconsistent finding for pulmonary consolidation which one would expect in that area rather than fluid or atelectasis. I am inclined to interpret this rather as pulmonary consolidation in view of the long respiratory wheeze, which could well be on the basis of partial bronchial compression. The abdomen was distended symmetrically, tympanitic, and without shifting dulness, indicative of at least partial intestinal obstruction. I would assume that it would be low down in the colon in view of the lower left quadrant pain at the onset. A liver palpable down three fingerbreadths must mean definite enlargement and suggests disease in the liver. The vague mass palpable in the left upper quadrant is probably not spleen from the description noted; I doubt that it is stomach in that location, it sounds too far forward to be kidney, and I would favor the impression of a metastatic implant or implants in the omentum of the left upper quadrant. The mass found in the left inguinal region apparently did not gurgle; it was firm, no impulse could be felt, and since it was reducible, I would interpret this also as being a metastatic implant attached close to the bowel or in the omentum, that slipped through the hernial ring.

The findings in the urine of one-plus albumin in every specimen examined, no increase in the usual number of red blood cells, casts, and even a few excess white blood cells, I believe only indicative of a nephrosclerosis in an individual sixty-two years of age. The anemia is microcytic and suggests a chronic blood loss or a chronic disease. The rapid fall in the hemoglobin from sixty-eight per cent down to twenty-five per cent must mean a hemorrhage from some source and in view of his course in the hospital, with blood in his stools, I assume that the bleeding is from the bowel. The rest of the laboratory findings are within normal limits and do not assist in the diagnoses other than in a negative way. I am very doubtful that the organisms in the sputum are of any significance. The admission scout film of the abdomen revealed no evidence of obstruction; however, the physical findings showed distension. The homogenous shadow described by x-ray in the upper abdomen is again suggestive of a neoplastic implant. The small oval nodule in the right mid-lung noted by chest x-ray, and elevation of the left leaf of the diaphragm are best explained by metastatic neoplasm of the lung, although this defect could possibly be primary bronchogenic neoplasm.

The fact that Wangensteen suction was established is further evidence in favor of some intestinal obstruction being suspected by the clinician. The findings of the ascitic fluid are very illuminating, and the culture being negative fairly well rules out the possibility of infection. Even though no neoplastic

cells were found in the fluid by centrifugation and blocking, I still would suspect that the fluid was due to neoplastic invasion of the peritoneum. The coffee-ground vomitus is further suggestion of at least partial obstruction with reverse peristalsis, and the finding of bright red blood, as well as tarry stools, probably explains the anemia and suggests disease low down in the colon in spite of the negative barium enema. Lesions of the rectal ampulla can be missed by the roentgenologist, particularly in a patient as sick as this one apparently was.

Clinical diagnoses:

- 1) Carcinoma of the colon (probably in the rectum or recto-sigmoid).
- 2) Metastasis to the peritoneum, liver and lung.
- 3) Nephrosclerosis.

Roentgenologic diagnoses:

- 1) Metastatic neoplasm of the lung.
- 2) Probable metastatic area in the abdomen.
- 3) Negative upper gastro-intestinal tract.
- 4) Negative colon.

Anatomic diagnoses:

- 1) Hypernephroma, left kidney, with metastases to the peritoneum, liver and lung.
- 2) Acute purulent bronchitis and bronchopneumonia.
- 3) Arteriosclerotic nephropathy.

Pathologist's comments: Dr. C. V. Weller: The clinician has drained this case dry from the standpoint of differential diagnoses, and his conclusions have been correct in every respect except for the location and type of the primary neoplasm. There is additional information which was withheld for obvious reasons. A peritoneoscopic examination was made two weeks before death and at that time a specimen was removed from the peritoneum for microscopic examination. A medullary carcinoma with vacuolar structure in some of its cells was found, and the pathologist commented that this was somewhat indicative of a hypernephroma.

At autopsy, the left kidney was found to be incorporated in a neoplastic mass which weighed 1200 grams and which was firmly attached to the spleen, pancreas and stomach.

The gastric and intestinal walls were heavily infiltrated by the neoplasm from the serosal side. This was especially true of the descending colon. This gives the probable explanation for both the coffee-ground vomitus and the severe hemorrhages from the bowel.



FRANK HOWARD LAHEY, M.D.

EDITORIAL

FRANK HOWARD LAHEY

THE FRIEDENWALD MEDALIST FOR 1946

The American Gastroenterological Association, through the generosity of Dr. Julius Friedenwald, has the opportunity each year to honor itself by conferring upon one of its members an award for distinction in the field of gastroenterology: this award being known as the Friedenwald Medal. This year, by the vote of the Governing Board, a surgeon has been so honored—Dr. Frank Howard Lahey. In my life, one singularly favored with pleasurable events, there has been no fuller gratification than the privilege which I have this evening in presenting this medal to you, Doctor Lahey, my guide and friend of so many years.

Your record of achievement is so widely known that it needs no emphasis on this occasion. Your contributions to the development of gastroenterology have been an important part of those achievements, and to us this evening they are of special interest. You will remember that in your younger years, during your metamorphosis from a promising to a brilliant surgeon, there was need for both development in technique in the surgery of the oesophago-gastro-intestinal tract, and for coordination of surgery with the newer gastroenterology which was being born of radiological and physiological developments. From your earliest days in surgery, developments in surgical technique could be counted as your forte—from the oesophageal diverticulum to the rectal carcinoma, if one proceeds anatomically through the gastro-intestinal tract, your surgical strategies and procedures will be passed on throughout generations of surgeons long after your individual skill and dexterity are lost to mankind. The generosity of your teaching to fellow, assistant, associate, and observer will live always in the memory of those surgeons who have been fortunate enough to come under your spell. By your labors, you have honestly earned the appellation—Peacemaker in gastroenterological surgery.

In those same early days of your surgical career, internist and surgeon were usually at war and medical meetings were the battlegrounds. There were battles over the hegemony of peptic ulcer and skirmishes over the diagnostic criteria of gallbladder disease. Violent verbal engagements took place in surgical or gastroenterological meetings and in the symposia which in those days only the fearless or the bloodthirsty dared to plan. Into this arena, you came not as the armored, embattled knight of surgery, but as the Peacemaker—the Peacemaker who by natural wisdom and growing experience pointed out the way of harmony and coordination—a form of beneficent collusion which has

resulted in countless advantages to both gastroenterology and surgery and to mankind in general.

As Peacemaker and Pacemaker, therefore, we greet you on this occasion.

I have mentioned your natural wisdom—that attribute of greatness which connotes the royal purple of the mind. Percipience, analysis, judgment, vision, imagination, were all there awaiting the development which followed naturally upon training and hard work; but this galaxy of gifts would have been useful but unlovely without the natural kindness of spirit with which Fate also blessed you. Those of us who have seen you minister with especial tenderness to the very young and the aged, with especial intensity and perseverance to the desperately sick, and with especial patience to the exasperatingly crotchety, know that in you human kindness gracefully complements natural wisdom.

All of us who have worked with you know that though greatness has been natural to you, it has likewise been earned by the sweat of your brow. To this day, we see an unfailing example of undaunted hard work, and with this hard work a modest subjective joy of accomplishment, which is at the same time both inspiring and intensely challenging to your friends and coworkers.

Nature gave you also that invaluable gift of precise expression without which wisdom so often goes undetected. Gradually throughout the years, your fame as a medical speaker has grown, and now your name on a medical program ranks as a star attraction. Your writings have been numerous—all through the years of work so engrossing that most doctors would have thought it impossible to add the burden of writing. Some of my pleasantest early impressions of our association have been of papers written jointly. You perhaps recall the incident in my pedantic days when I apparently thought well of my diction and I suggested that you should pronounce the adjective characterizing oesophagus with an antepenultimate accent—oesophágeal—since that was preferred. You went to the middle west and gave a paper on diverticulum of the oesophagus, and following my suggestion, used the very correct pronunciation. One of the discussors said that his interest in the substance of the paper was constantly diverted by the very strange pronunciation of the word oesophageal, but he supposed, since Doctor Lahey came from Boston, he must know what he was saying. You told me of this incident with what I thought was considerable disillusionment, and said that from now on you would pronounce oesophageal as everyone else did. Shortly thereafter you went to Baltimore and gave the same paper, using the adjective with its popular accent. Doctor Finney in his discussion said he was interested in the substance of the paper, but he was surprised that a man from Boston should pronounce the adjective oesophagéal and not oesophágeal.

These last few weeks have brought you a triad of honors, the Legion of Merit, the Bigelow Medal, and this evening the Friedenwald Medal of the American

Gastroenterological Association—surely a stalwart sheaf of laurels upon which to rest. In the case of our medal, while it is our custom to award it to our elder men of distinction, the implication is not at all that it is time to rest. The world still awaits your contributions to all fields of surgery, and we of the American Gastroenterological Association expect of you a continued and prolific interest in gastro-intestinal disease. For we know that you belong to that youth so well characterized by an unidentified author who says "Youth means a predominance of courage over timidity, of the appetite of adventure over the love of ease. People grow old by deserting their ideals." Because you have fulfilled your ideals and could never desert them, the American Gastroenterological Association presents to you, Frank Howard Lahey, the Julius Friedenwald Medal.

SARA JORDAN

FRANK HOWARD LAHEY

The news of the award of the Friedenwald Medal of the American Gastroenterological Association to Dr. Frank Howard Lahey will be received with pleasure by the readers of *GASTROENTEROLOGY*. Dr. Lahey has appropriately received many honors for his services to the Profession and his contributions to Surgery. He has been a faithful member and has contributed freely to the scientific sessions of the Association.

His numerous contributions to the surgery of the digestive tract have caused him to be known as one of America's outstanding surgeons. In the field of graduate education no one is better known as a teacher. This is because he impresses everyone with the thoroughness of his grasp of the subject and the earnestness and excellence of his presentation. He has given freely of his time to improve the quality of surgical diagnosis and procedure. He has enthusiastically accepted some of the broader responsibilities of his profession by serving on the Council on Medical Education and Hospitals and as Chairman of the Board of Procurement and Assignment of Physicians for Selective Service during World War II.

Dr. Lahey's delightful personality, his modesty and approachableness account for his many fond friends and for the affectionate esteem of everyone who has had the good fortune of discussing medical subjects with him.

He has honored the profession and the profession is pleased to honor him.

A. C. I.

COMMENT

HISTAMINE AND GASTRIC SECRETION IN RELATION TO ANTI-HISTAMINE DRUGS

The appearance of a number of new synthetic drugs which are able to counteract certain of the pharmacological effects of histamine renews interest in the subject of the possible rôle of histamine formed within the body as a stimulant of gastric secretion in health and disease.

Confusion exists in regard to the possible relation of histamine to the gastric hormone, gastrin, which is released by the pyloric mucosa when secretagogues are in contact with it. Numerous acid extracts of pyloric mucosa have been made which exhibit a potent stimulatory effect on gastric secretion when administered in relatively small doses subcutaneously. Two questions arose in regard to these extracts, namely, (a) What is the active ingredient? and (b) Is this the same substance which is released by the gastric mucosa when secretagogues act upon it?

The first question was definitely answered by Sacks and co-workers (1) when they demonstrated that crystalline histamine could be recovered from these extracts and that destruction of the histamine in the extracts abolished their stimulatory action on gastric acid secretion. The second question cannot be answered with certainty. The evidence in favor of the view that histamine is the hormone released by the pyloric mucosa consists of the demonstration of its presence in the mucosal extracts and its well-known high potency as a gastric secretory stimulant. There are, however, several objections to the acceptance of histamine as the true gastrin. The most serious objection is based on the evidence obtained by the use of atropine. Whereas atropine in a dose of 1 milligram is able to completely abolish the gastric secretory response to a meal in the dog, the same dose produces only partial inhibition of histamine induced gastric secretion. These facts indicate that either atropine is able to prevent the release of histamine or histamine is not gastrin. A further objection to the view that histamine and gastrin are identical is found in the fact that histamine can be extracted from a large number of tissues in the body, for example the concentration in the fundic mucosa is even higher than that of the pyloric mucosa, thus casting doubt upon its specificity as the pyloric hormone.

Attempts to detect an increase in blood histamine concentration during the secretory response to a meal have been unsuccessful. These studies do not, however, provide evidence for or against the identity of histamine and gastrin inasmuch as it is known that doses of histamine too small to produce a measurable rise in blood histamine level can produce a marked stimulation of gas-

tric secretion. In other words the gastric glands are more sensitive to histamine than are the methods at present available for its measurement in the blood.

Because of the doubt regarding the identity of histamine and gastrin, several investigators have attempted to prepare histamine free extracts of the pyloric mucosa with gastric secretory stimulatory activity. Komarov (2) and more recently Uvnäs (3) have reported that extracts can be prepared which give none of the reactions for histamine but still are able to stimulate gastric secretion upon intravenous administration. Because of a certain inconstancy in the effectiveness of these extracts in producing gastric secretion and because in our own laboratory several attempts to prepare such extracts have been unsuccessful, further studies on this important problem are needed.

Should the existence of a histamine-free pyloric mucosal extract with potent gastric stimulatory action be adequately confirmed, then the suspicion that histamine does not answer all the requirements of the true gastrin will have been proven to be well founded. Although the final word has yet to be spoken, the weight of evidence now available indicates that histamine is not gastrin and that histamine may be released by the gastric and intestinal mucosa only when the mucosa is irritated mechanically or chemically.

From several quarters has come another suggestion as to a possible rôle of histamine in stimulating the gastric parietal cells in the normal body economy. First Babkin (4) and Mac Intosh (5) and now Emmelin and Kahlson (6) have propounded the hypothesis that histamine may act as a chemical mediator or "local hormone" in the gastric secretory process. Finding that gastric juice collected during the cephalic phase contained more histamine than did the blood plasma, the former investigators suggested that during the cephalic phase histamine is liberated within or near the parietal cells as a result of stimulation of the vagus nerve. The latter researchers extended this concept to include the gastric phase of secretion, suggesting that the pyloric hormone also caused the local release of histamine which stimulated the parietal cells and was secreted by them into the gastric juice. The high histamine and low histaminase content of the fundic mucosa is considered to lend support to this hypothesis. If such a mechanism actually operates, it must be postulated that none of the histamine released locally enters the venous blood leaving the stomach because it is well known that a Heidenhain pouch will not respond to sham feeding during which period the main stomach is actively secreting. For this reason the hypothesis is not readily acceptable.

The third way in which histamine may be involved in gastric secretory mechanisms is in certain pathological states. Ivy and Bachrach (7) suggested that the acid secretion which cannot be abolished by atropine in the Mann-Williamson dog might be due to a histaminergic type of stimulation inasmuch

as histamine is the only known stimulant whose effect cannot be abolished by atropine in the dog. The irritated mucosa at the site of the ulcer may be the site of release of this histaminic stimulus. A similar mechanism may operate in some men and women with duodenal ulcer in whom, unlike normal persons, atropine in doses of $\frac{1}{40}$ grain does not abolish the interdigestive secretion.

None of the anti-histamine drugs so far tested have shown a significant inhibitory effect on the gastric stimulating action of histamine. It will be apparent from this cursory survey that if a drug should be found which is able to counteract the action of histamine on the gastric glands it could not be predicted with certainty what the effect of that drug would be upon the secretory activity of the normal or diseased stomach. Nevertheless the search for such a drug does and should continue apace because when it is discovered it will help us to answer some of the perplexing questions discussed above and it may well prove to possess therapeutic worth.

M. I. G.

A. C. I.

REFERENCES

1. SACKS, J., IVY, A. C., BURGESS, J. P., AND VAN DOLAH, J. E.: Am. J. Physiol., **101**: 331, 1932.
2. KOMARVI, S. A.: Revue Canad. Biol., **1**: 377, 1942.
3. UVNAS, B.: Acta Physiol. Scand., **4**: Suppl. 13, 1942; *ibid*, **6**: 97, 1943.
4. BABKIN, B. T.: Canad. Med. A. J., **38**: 421, 1938.
5. MCINTOSH, F. C.: Quart. J. Exper. Physiol., **28**: 87, 1938.
6. EMELIN, N., AND KAHLSON, G. S.: Acta Physiol. Scand., **8**: 289, 1944.
7. IVY, A. C., AND BACHRACH, W. H.: Am. J. Digest. Dis., **7**: 76, 1940.

OBSERVATIONS ON THE HEALING OF GASTRIC ULCERS

An excellent discussion of the changes in the roentgenologic appearance of the stomach during the healing of peptic ulcer has been published by Templeton (1). He and his colleagues made simultaneous roentgenologic and gastroscopic observations of gastric ulcers during medical treatment and concluded that when the roentgenologist notes a disappearance of the crater, the gastroscopist is likely to report that the lesion is healed or almost healed. Templeton discussed the rôle of subsiding edema and of contraction of scar tissue in altering the appearance of large gastric craters as viewed in successive roentgenograms during medical treatment. He felt, however, that there is likely to be a discrepancy between the roentgenologist's, the gastroscopist's and the pathologist's description of a given ulcer. This is because the roentgenologist sees usually a profile of a silhouette, the gastroscopist sees the ulcer through an instrument which diminishes the apparent depth and size of the lesion, and the

pathologist sees the lesion in three dimensions. The latter is of course the true picture.

It has been suggested by Ivy (2) that the mechanism of healing of a peptic ulcer, a process which the clinician cannot ordinarily follow by direct observation, may well be visualized in terms of the healing of an ulcer of the skin, a process with which every physician is familiar. The analogy is valid because it has been established that the sequence of biological phenomena is qualitatively and quantitatively similar in the two cases.

The surprise which we physicians sometimes express when there is a rapid diminution in size of a large crater on the lesser curvature of the stomach is due to our lack of acquaintance with the mechanism of the healing of such lesions. When treatment enables a peptic ulcer to start healing, the lesion is reduced rapidly in size within a few days by a process of contraction similar to that which occurs in the healing of an ulcer in mobile skin. This contraction usually continues until the ulcer is somewhat smaller than 1.5 cm. in diameter, and hence there is a tendency, at the start of healing, for all large ulcers to be reduced rather rapidly to this size. And, since the rate of contraction is proportional to the initial size of the lesion, it becomes apparent why the larger the ulcer at the beginning of treatment, the more spectacular will seem its rate of healing.

Since the initial rapid reduction in the size of a large crater is due mainly to contraction, the subsequent relatively slow rate of disappearance of the defect due to epithelialization does not, by itself, justify a roentgenographic or gastroscopic diagnosis of probable malignancy. A large benign ulcer which, when first seen, was much feared because of its size, may be less feared during the later stages of its healing if it is understood that the fleck of barium which is seen for a while is in the center of a stellate scar and not in a "residual crater."

When a benign ulcer does not heal, it may be because its floor is composed of dense scar tissue which cannot contract and over which neither granulation tissue nor epithelium can creep. Eventually, the epithelium at the borders ceases to proliferate, and the margins flatten. This lesion appears much less threatening roentgenographically than the deep, punched-out ulcer with heaped-up margins, which occasions surprise in everyone by its seemingly miraculous disappearance. The former lesion has exhausted its healing potential; the latter has not.

With further advances in diagnostic technic, particularly with respect to gastroscopic visualization, it may become possible to determine more accurately from the size and appearance of an ulcer whether it is likely to heal under adequate medical management, and how soon healing can be expected. It is to be regretted that no report has yet been made of studies designed to determine the

rate of healing of peptic ulcers. With such information at hand it may be possible to compare different therapeutic regimens not only in qualitative terms of whether or not they bring about healing, but in quantitative terms of how efficiently they do this.

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REFERENCES

1. TEMPLETON, F. E.: X-ray Examination of the Stomach. University of Chicago Press., 1944.
2. IVY, A. C.: Personal communication.

BOOK REVIEWS

ALTERACOES HEPATICAS NA TIREOTOXICOSE. *By P. A. da Costa Couto.* Printed for the author. Rio de Janeiro, 1944.

This book of 278 pages is an important contribution to the study of thyrotoxicosis. Dr. Costa Couto emphasizes what has been known to pathologists for years and that is the persons dying of exophthalmic goiter commonly have a liver which is largely destroyed and replaced by fat. Knowing this and faced with a patient with long-lasting thyrotoxicosis, the physician will do well to study the liver function. If the tests should show a marked defect in function, it might be wise before operating, to prepare the patient with a low-fat, high carbohydrate diet.

AMBULATORY PROCTOLOGY. *By A. J. Cantor.* Published by Paul B. Hoeber, Inc., New York, \$8.00. 524 pages.

This is an attractive book, well written, well illustrated, and well published. It is full of useful and detailed information. There is a good chapter on anesthesia and another unusual one on pediatric proctology. There is much on that bugbear of the physician—pruritus ani, and its treatment by tattooing is described in detail. There are several chapters on diseases of the colon, and good bibliographies are appended to every chapter.

About the only criticism which occurs to the reviewer is that in a book entitled *Ambulatory Proctology* there is so little on the care of the patient after operation. Chapter IV, which deals with this subject, is much too short. Perhaps, in a later edition much will be added until this is the longest and most important chapter in the book. At the end of the chapter on hemorrhoidectomy one looks in vain for a few words on the extremely important postoperative care of the patients. According to some proctologists, the postoperative care is as important as the operation. But mention of these omissions should not obscure the fact that this is an attractive and useful book.

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STOMACH

SOMMERVELL, T. H. The operation of ligation of the arteries of the stomach to relieve hyperacidity and to prevent recurrent ulceration after gastro-enterostomy. *Brit. J. Surg.*, 33: 146 (Oct.) 1945.

The operation of ligation of a large proportion of the arteries supplying the stomach is described. This operation leads to the cutting down of hyperacidity to normal levels, and sometimes below. It is hardly ever followed by recurrent ulceration, and the reduction of acidity is permanent, at least for 5 or 6 years; in this respect it is superior to that obtained by gastrectomy. It is believed that this is the operation of choice in all cases of duodenal ulcer with marked hyperacidity, and it can easily be combined with gastroenterostomy, without raising the mortality of this operation.

FRANZ J. LUST.

CARDON, L. AND GREENEBAUM, R. S. Lymphosarcoma of the stomach. *Am. J. Dig. Dis.*, 12: 339 (Oct.) 1945.

These clinicians reported a case of lymphosarcoma of the stomach in which the outstanding features were: fever; a mass in the abdomen resembling Riedel's lobe; a spleen the tip of which was just palpable at the costal margin; tenderness over an indistinct mass in the epigastrium; an irregular, poorly filled stomach with carcinoma-like termination of the defect at the pylorus; achlorhydria; occult blood in the stool; and non-visualization of the gall bladder.

H. J. SIMS.

BOWEL

Foss, H. L. Carcinoma of the colon in rural Pennsylvania. *Penn. Med. J.*, 49: 17 (Oct.) 1945.

The interval between the onset of symptoms and correct diagnosis averaged over 8

months in this series of cases with carcinoma of the colon. The unfavorable condition in rural areas regarding diagnostic means, and the accessibility of such diagnostic procedures as are available, account for this delay. Most patients had advanced metastases and were inoperable at the time of admission. The initial symptoms were either taken too lightly by the patient or erroneous diagnoses were made. The most important initial symptom in carcinoma of the rectum was diarrhea, usually alternating with constipation. Colicky pain and later obstruction, were the main symptoms in the other forms of colonic cancer. Some details are worth emphasizing: most cancers of the rectum can be felt with the index finger; 70% of all rectal cancers are of low malignancy. The author used the one-stage abdomino-perineal resection in carcinoma of the rectum, and resection with end-to-end anastomosis in carcinoma proximal to the recto-sigmoid.

MANFRED HESS.

MEYER, K. A., SHERIDAN, A. AND KOZOLL, D. D. One stage "open" resection of lesions of the left colon without complementary colostomy. *Surg. Gyn. Obs.*, 81: 507 (Nov.) 1945.

A preliminary report is presented of 20 cases of one stage resection of the left half of the colon by an "open" technique, in which there was a mortality of 5%. Requirements to be satisfied before this procedure is undertaken include: administration of succinylsulfathiazole, adequate blood transfusion and/or amino acid therapy, intragastric suction siphonage, oxygen inhalation, an anesthetic agent with a quieting effect on the gastrointestinal tract, and use of fine permanent interrupted sutures in bowel and wound.

Advantages of the one stage resection, without complementary colostomy include: (1) more radical resection of the tumor; (2) obviation of complications inherent in exteriorization procedures; (3) avoidance of a colostomy; (4) shortened postoperative course and fewer re-admissions. This procedure should not be attempted in the presence of a distended colon, in lesions fixed close to the pectinate line of the rectum, in

presence of infection, and in a patient with a short mesentery.

FRANCIS D. MURPHY.

SMITH, O. A. Intussusception—diagnosis and treatment. *Am. J. Surg.*, 70: 158 (Nov.) 1945.

Intussusception is the invagination or indigitation of a segment of the intestine into an adjacent portion and was first described by John Hunter in 1789. The four varieties are: (1) ileocecal, (2) colic, (3) ileal or jejunal, and (4) ileocolic. In this series of 35 cases, the mortality for the 31 operated upon was 16.1%. The ages ranged from 5 weeks to 60 years, and the sex incidence was 68% males and 32% females. The etiology remains relatively obscure, particularly in the infant group; a cause was nearly always found in adult cases. The ileocecal or ileocolic variety formed 50% of the entire group, which included 5 cases of multiple intussusception.

Subjective and objective symptomatology in the series shows no remarkable variation from the classical picture. The most constant findings were nausea, vomiting, pain, and an abdominal palpable mass. A rectal examination exposed masses in 3 cases where none were palpable on the abdomen. Surgical therapy in each of the 31 patients operated upon consisted of reducing the intussusception from below upward, in all cases except the eight resected. The practice of traction on the proximal loop of bowel is to be condemned, and if the mass cannot be reduced by gentle pressure, the possibility of the need for resection must be given immediate consideration. The incidence of recurrent intussusception is low and did not definitely appear in this series.

MICHAEL W. SHUTKIN.

RENSHAW, R. J. F. AND BROWNELL, T. S. Carcinoma complicating ulcerative colitis. *Cleveland Clinic Quart.*, 12: 123 (Oct.) 1945.

Two patients are described, a man aged 22 and a woman aged 27, in whom carcinoma of the colon appeared as a complication of ulcerative colitis. This combination is rare. At the Cleveland Clinic these were the only cases encountered in a 9 year period.

This gave an incidence of 0.59% of all cases of chronic ulcerative colitis and of 1.5% of cases in patients under 30 years of age at this institution.

IRVING WOLMAN.

PFEIFFER, D. B. AND PATTERSON, F. M. S.

Congenital or hereditary polyposis of the colon. *Ann. Surg.*, 122: 606 (Oct.) 1945. The authors review current concepts regarding multiple polyposis of the colon and report their experience with 5 such patients. Four of these had family histories of polyposis or carcinoma of the colon. The recommended three-stage surgical treatment is (1) fulguration of polyps in the rectum and terminal sigmoid, (2) ileorectosigmoidostomy, and (3) colectomy.

LEMUEL C. McGEE.

MUELLER, R. S. The local use of sulfanilamide in the treatment of acute appendicitis. A review of 1481 cases.

Ann. Surg., 122: 625 (Oct.) 1945. Mueller reviews the experience of the surgical service of the Roosevelt Hospital with acute appendicitis during the past decade. From 1935 to 1939 there were 742 cases with 21 deaths (2.83%) from acute appendicitis, abscess, or peritonitis. From 1940 to 1944 there were 739 cases with 3 deaths (0.40%). Chemotherapy is given the chief credit for the lower mortality in recent years. The use of sulfanilamide in the peritoneal cavity is preferred to its oral or intravenous use in patients with peritoneal contamination. No serious toxic effects followed the use of sulfanilamide in this manner. Drainage and the use of penicillin postoperatively are recommended.

LEMUEL C. McGEE.

ALTEMEIER, W. A. Diverticulitis of the veriform appendix. *Am. J. Surg.*, 70: 258 (Nov.) 1945.

This report concerns a case of appendiceal diverticulosis with superimposed subacute inflammation. The patient was a white, married female of 22 years who was exposed to appendectomy after 3 weeks of observation for suspected mesenteric lymphadenitis. At operation, a large appendix with multiple diverticulae were found, and in 2 of the sacs

inflammatory changes were present. Though diverticulosis is common to the intestinal tract, diverticula rarely occur in the veriform appendix. The multiple diverticula in this case were apparently of the true congenital type.

MICHAEL W. SHUTKIN.

AMSTERDAM, H. J. AND GRAYZEL, D. M.

Intestinal lipodystrophy (lipophagia granulomatosis or Whipple's disease). *Am. J. Med. Sci.*, 210: 605 (Nov.) 1945.

The authors describe an instance of intestinal lipodystrophy (lipophagia granulomatosis or Whipple's disease), presented as the 14th such case to be reported. The clinical picture is similar to that of sprue; the postmortem findings determined the diagnosis in this as in the other cases.

The patient was a Jewish man, 54 years of age, who had suffered for more than 2 years with recurring bouts of diarrhea, postprandial abdominal distension and discomfort, anemia, weight loss and asthenia. Roentgen ray studies showed changes in the gastrointestinal tract which were interpreted as representing a deficiency pattern and probably a regional ileitis of the terminal ileum. At necropsy the diagnostic findings were thickening of the valvulae conniventes, and mesenteric lymphadenopathy with lipid deposits in the nodes. The sections for microscopic study showed enlarged intestinal villi and necrosis of the mucosa. The jejunal mucosa and mesenteric lymph nodes contained foamy, fat-laden macrophages. The cause of the disease is unknown.

LEMUEL C. McGEE.

PUGH, H. L. Regional enteritis. *Ann. Surg.*, 122: 845 (Nov.) 1945.

Pugh reviews 17 instances of regional enteritis seen in a Naval Hospital. The patients, all males, varied from 17 years to 33 years in age. There is no information as to the course of the disease after the patients left the hospital.

Abdominal pain (usually in the right lower quadrant), intermittent diarrhea, and loss of weight were the cardinal symptoms. Anemia and fever were the common findings during an acute phase. In 10 of the 17

cases the roentgenologic "string sign" of Kantor was observed. Fourteen of the patients received a surgical resection of the involved bowel with an ileocolostomy. In 9 patients, the pathologic process extended into the colon from the ileum. There was one death, presumably from suppression of renal function. Three patients "cleared up without definitive surgery."

LEMUEL C. McGEE.

TAYLOR, A. W. Chronic hypertrophic ileocaecal tuberculosis, and its relation to regional ileitis (Crohn's disease). *Brit. J. Surg.*, 33: 178 (Oct.) 1945.

A review is given of the etiology, pathology, and histology of Crohn's disease and hypertrophic ileocaecal tuberculosis. The author draws attention to the fact that it is impossible, on a basis of clinical features or morbid anatomy, to distinguish between the two conditions. Three cases of ileocaecal tuberculosis are described. A chronic tuberculous mesenteric lymphangitis is described in one of the cases: the wall of the affected ileum in this case showed the gross pathological and the histological features described as characteristic of Crohn's disease. It is suggested that a similar chronic lymphangitis of the mesentery may be the basis of many cases of regional ileitis where the lesions in the affected gut wall are apparently non-tuberculous.

FRANZ J. LUST.

MELAMED, A. Volvulus of megacolon reduced during barium enema examination. *Radiol.*, 45: 392 (Oct.) 1945.

A case of mechanical intestinal obstruction due to volvulus of a sigmoid megacolon, reduced by barium enema, is presented. The roentgenological examination of the abdomen in the recumbent and upright positions on the day of admission to the hospital showed great distention of the large intestine, apparently down to about the level of the distal descending or sigmoid colon. The right half of the colon contained a considerable amount of fecal material. Marked dilatation and elongation of the overlapping and distended loops of large bowel were observed. A few loops of small intestine were seen to contain small quan-

tities of gas, irregularly distributed. In the upper abdomen a few fluid levels were demonstrated, but there was no evidence of free gas in the peritoneal cavity. The barium enema examination revealed almost complete obstruction in the sigmoid region. The mucosal pattern indicated rotation or twisting of the large bowel in this region. As more opaque substance was carefully injected, untwisting occurred and the obstruction was gradually relieved and reduced. Filling of the entire colon then became possible, but nearly two gallons of barium suspension was necessary for this, indicating the presence of a megacolon.

FRANZ J. LUST.

DENNIS, C. Ileostomy and colectomy in chronic ulcerative colitis. *Surgery*, 18: 435 (Oct.) 1945.

The author quotes earlier statistics indicating that at the University of Minnesota there was an 8% mortality among 25 patients with chronic ulcerative colitis treated surgically, whereas the mortality among 57 patients treated conservatively was 28%.

It is advised that only the very mild cases of ulcerative colitis be treated medically, and that the fulminating ones and the moderately severe ones with remissions be treated by ileostomy. Ileostomy is also advised as an emergency procedure in uncontrollable hemorrhage, fulminating infection, impending perforation, and obstruction. It may also be advisable in very early colitis or in most patients who have polyposis. A technique for single-barrelled ileostomy is described in detail, both regarding the operation itself and the care of the ileostomy stoma.

It is advised that colectomy follow ileostomy if profuse discharge continues, if there is profuse hemorrhage, if there is more than one exacerbation of colitis after the ileostomy, and if polyps or carcinoma of the colon exists. Colectomy is deferred 5-6 months after the ileostomy in order to minimize the risk. The colon is removed down to the recto-sigmoid and the rectum is then observed periodically by proctoscopic examination. A new method for closing the rectal stump at the time of the colectomy is described. In cases where solid stools are

passed from the ileac stoma, and the rectal mucosa becomes normal in appearance, it may be possible to perform an ileoproctostomy. This has been done in 6 cases to date.

HENRY TUMEN.

McLANAHAN, S. AND JOHNSON, M. L. Spontaneous rupture of lower colon with evisceration of small intestine through the anal orifice. *Surgery*, 18: 478 (Oct.) 1945.

The author reports the case of a 76 year old woman with rupture of the sigmoid colon and spontaneous evisceration of the small intestine through the anal orifice. Six additional similar cases were reviewed and it is noted that in 5 of these, as well as in the case here reported, rectal prolapse was a pre-existing condition. Therefore it seems that rectal prolapse is an etiologic factor in the occurrence of this type of evisceration. When prolapse exists, the intra-abdominal pressure can be directed against the anterior wall of the rectum or colon with sufficient force to cause its rupture.

HENRY TUMEN.

HADDON, J. W. L. A case of left-sided appendicitis. *Brit. Med. J.*, 4425: 569 (Oct.) 1945.

A case of left sided appendicitis is reported in a male aged 19. At operation, the iliac fossa was filled with distended coils of the small intestine. The cecum occupied the left iliac fossa. There was a long gangrenous appendix lying obliquely across the lower abdomen from left to right. There was no evidence of inflammatory adhesions or other changes indicative of inflammation, but a band was found in the ascending colon, which was considered of congenital origin in non-rotation of the mid-gut.

MAURICE FELDMAN.

FULTON, M. Gram-negative intestinal bacilli from the southwest: Identification of 400 cultures. *South. Med. J.*, 38: 693 (Oct.) 1945.

A Salmonella typing center was established in Dallas in 1939, officially recognized and furnished with typical cultures and serums by the Copenhagen laboratory. The author

presents a review of the identification made of 400 consecutive cultures submitted to this center during 1943. Typhoid, dysentery, gastro-enteritis in general, as well as such extra-intestinal infectious processes as cystitis, abscess formation, and septicemia, all have been considered. The only limitation imposed has been that cultures studied should be the gram-negative rods commonly known as the intestinal bacilli. The typhoid, paratyphoid, and food poisoning types are studied in detail by serological methods. Typhoid bacilli, 24 strains in all, are included in *Salmonella* because of antigenic relationships. In many of these generic groups there is at present no satisfactory subdivision into species. All appear to be more or less capable of producing febrile illnesses, acute gastro-enteritis of food-borne origin, and a variety of systemic or local nonspecific processes, from septicemia to abscess formation. There is more or less tendency to the establishment of the carrier state following either overt or unsuspected infection with these organisms. The *Salmonella* group was of special interest because methods of identification have been carried to a high degree of refinement, the strains examined including 83 from Texas. Paratyphoid A bacillus has not been observed. A noteworthy feature of this series of *Salmonella* cultures is the large number, 42, of "group C" strains which it includes. The *Salmonella* C group corresponds roughly to what was formerly referred to as the "hog cholera group." The large proportion of group C strains in this series cannot be precisely accounted for. It has been shown that group C *Salmonella* types are prone to cause extra-intestinal infection, frequently without associated intestinal symptoms or demonstrable intestinal pathology. The morbidity reports of the Texas Commissioner of Health show large numbers of cases of dysentery, but few of *Salmonella* infection. Among 400 cultures classified by the *Salmonella* Typing Center, 158 were *Salmonella*, 53 *Shigella*, 47 *Paracolon*, 46 *Proteus*, 31 *Morganell*, 28 *Coliform*, and 44 in the groups *Eberthella* (not the typhoid bacillus), *Pseudomonas*, and *Alkaligenes*.

IRVING GRAY.

LIVER AND GALL-BLADDER

WALTON, J. The aetiology of gall-stones. *Brit. Med. J.*, 4426: 593 (Nov.) 1945. For the purpose of etiology, gall stones are classified as cholesterol, pigment, mixed, and calcium carbonate stones. Cholesterol stones are usually single and occur more commonly in married women. It was found that these stones were associated with cholecystitis. The pigment stones are biliverdin calculi, small and irregular, and dark in color. The pure stones are soft and putty-like. These stones may be found in the ducts or in the gall bladder. The pigment stones are found with extensive blood destruction, as in acholuric jaundice, malaria, etc. They are metabolic in origin and due to deposition from a supersaturated solution. Mixed stones, the most common variety, may be single or multiple. When single and large, they are prone to ulcerate through the fundus into the duodenum; when multiple, they may fill the gall bladder. One of the characteristics of this group is their lamination. There is considerable controversy regarding the method of formation of these stones: (a) stagnation of bile, (b) metabolic changes, (c) constitutional susceptibility, (d) neurogenic dysfunction, and (e) infection. Calcium carbonate stones are the most interesting variety and most difficult of explanation. They are generally small and relatively few in number.

MAURICE FELDMAN.

JALLING, O., LAURSEN, T. AND VOLQVARTZ, K. Studies of serum phosphatase activity in relation to experimental biliary obstruction in rabbits. I. *Acta Physiol. Scand.*, 10: 70 (Aug.) 1945.

A number of theories have been suggested as to the mechanism of the increase in serum phosphatase activity in obstructive jaundice. One theory is that the hyperphosphatasemia is due to retention of phosphatase which is normally excreted by the liver in the bile. Others have suggested that the hyperphosphatasemia is due to an activation of the normal serum phosphatase rather than to an actual increase in the amount of

circulating phosphatase. A third theory suggests that the hyperphosphatasemia is due to an absence of bile in the intestine which presumably is followed by disturbance in the calcium-phosphorus metabolism. The problem concerning the mechanism of the development of hyperphosphatasemia in obstructive jaundice was taken up for renewed examination on rabbits, which have been found suitable for such experiments.

The increase in serum phosphatase after ligation of the common bile duct starts immediately and reaches a maximal value 15 to 20 times greater than the normal value in about 15 hours, followed by a slow drop during the next days. The increase in serum phosphatase is a real rise in the amount of the enzyme. However, it is not released from the common bile duct. The results of the experiments do not support the "activation theory," nor can they be explained by the absence of bile in the intestine. The retention of bile phosphatase alone cannot explain the hyperphosphatasemia.

ALBERT CORNELL.

GOLDMAN, B., JACKMAN, J. AND EASTMAN, R. H. The management of postoperative choledocholithiasis. Another use for solution G. *Surg. Gyn. Obs.*, 81: 521 (Nov.) 1945.

Several unsatisfactory experiences in the management of postoperative choledocholithiasis led to a search for a substance which would act directly upon the retained calculi and reduce them chemically. The criteria for such a substance are as follows: (1) it should be a liquid, which is non-toxic and readily made or easily obtainable; (2) it must bring about chemical reduction of cholesterol and calcium salts. The work of other investigators with solution G in the dissolution of urinary calculi suggested itself since; like urinary incrustations and concretions, gall-bladder and common duct stones also contain calcium. Since bilirubin-calcium stones are the most common variety, solution G should theoretically be chemically effective on a large proportion of common duct stones.

Upon postoperative cholangiography, 2

patients were found to have retained common duct stones. Solution G was administered, without discomfort of any kind. The patients expressed a feeling of well-being after instillation of the first 1000 cc. There was no pain. A mild diarrhea occurred in one case; in both the stools were green in color. Clinical results were excellent, but in vitro experiments, conducted later, were disappointing.

FRANCIS D. MURPHY.

BRUNSCHWIG, A. AND BIGELOW, R. R.
Advanced carcinoma of the extrahepatic bile ducts: Choleangiocholecystocholecystectomy. *Ann. Surg.*, 122: 522 (Oct.) 1945.

Brunschwig observes that extensive carcinomatous involvement of the gall bladder, common bile duct, and hepatic ducts creates one of the most hopeless situations which can confront a surgeon. He describes a technic for radical resection of these structures with the insertion of two T-tubes, one in the stump of each hepatic duct, and the insertion of the lower arms together in the stump of the common duct. Four of 7 patients so treated survived operation for 3-12 months. The chief benefit to the patient is that of relief from icterus and pruritis.

LEMUEL C. McGEE.

MIGIACCIO, A. V. Reconstruction of the common duct with vitallium tubes. *Am. J. Surg.*, 70: 261 (Nov.) 1945.

Since the introduction of the vitallium tube in the reconstruction of the common duct, the problem of pressure by this tube on the adjacent blood vessels has arisen. The case reported here in great detail answers this question and points out some unusual experiences, such as: (1) the accidental and fortunate establishment of an abdominal biliary fistula by surgery, just at the time that the patient was on the verge of establishing his own bronchobiliary fistula; (2) the necessity for having many types of vitallium tubes ready on the operating floor; (3) the establishment of a gastrohepatic biliary fistula with rubber tubes, which was blocked by the rotting away of one of the rubber tubes; and (4) the successful reestab-

lishment of the normal connection between the two hepatic ducts and the distal end of the common duct with the aid of a "Y" shaped vitallium tube.

The common duct had been severed during a previous cholecystectomy and the author reestablished bile continuity after 3 operations. Since his discharge and up to the present, a period of 24 months, the patient has remained well.

MICHAEL W. SHUTKIN.

HOAGLAND, C. L. The therapy of liver diseases. *Bull. N. Y. Acad. Med.*, 21: 537 (Oct.) 1945.

This discussion is limited principally to a consideration of the most important non-obstructive, non-malignant diseases of the liver. Until there is better information concerning the nature of the various etiological factors at work in liver disease, one can accomplish more in therapy by devoting attention chiefly toward those measures which hasten repair of the damaged liver, regardless of the nature of the agent or process initiating the disorder.

Using Bloomfield's classification, the variations which may occur in the course of hepatitis are represented by: (1) Acute hepatitis progressing rapidly to death, referred to as acute yellow atrophy in the older terminology. (2) Acute hepatitis with apparent recovery but with actual transition to a latent stage, with or without remissions. If clinical recovery does not follow, this may develop into a fibrotic stage, which is commonly referred to as cirrhosis. (3) Those cases in which hepatitis is latent from the start, and is masked clinically until incipient liver insufficiency supervenes. Therapy should be concerned mainly with a consideration of the stage of hepatitis, i.e., whether it be acute, sub-acute, or chronic in its clinical manifestations. The once familiar syndrome of "catarrhal jaundice" is identical with acute infectious hepatitis or epidemic jaundice, as it is now commonly called.

Therapy here is directed to measures which are believed to hasten repair of the damaged liver parenchyma. If an adequate intake of protein and carbohydrate is provided, there is no good evidence that inclu-

sion of moderate amounts of fat is harmful. Further reports on the use of sulphur amino acids, notably methionine, are awaited. Bed rest, or at least limited activity, appears to be of paramount importance. To maintain nutrition, carbohydrates and amino acids may be given intravenously as a mixture. Chronic liver disease may develop in a small number of patients after a severe or prolonged attack of acute infectious hepatitis. Chronic liver disease with insufficiency still presents one of the most complex problems of therapy. The rôle of alcohol in the production of cirrhosis is still anything but clear. The high carbohydrate and protein, moderate fat, diet is the diet of choice. Parenteral vitamins may also be indicated, as there is definite faulty metabolism of vitamins A, D, and K, especially. There is also aberrant metabolism of hormones in cirrhosis. In patients with ascites, there is an antidiuretic substance excreted in the urine, arising presumably from the posterior pituitary gland.

There is some reason to regard cirrhosis of the liver as an intrinsic deficiency disease. To relieve these deficiencies, the author describes a new method of giving liver extract intravenously as replacement therapy in hepatic insufficiency, with encouraging preliminary results.

ALBERT CORNELL.

GYÖRGY, P. AND GOLDBLATT, HARRY.
Thiouracil in the prevention of experimental dietary cirrhosis of liver. *Science*, 102: 451 (Nov.) 1945.

Data were tabulated for experiments with two groups of rats, receiving the same diet, one group being supplemented with thiouracil. It was evident that admixture of thiouracil to a basic cirrhosis-producing synthetic diet exerts a marked preventive effect, manifesting itself in (a) a much lower incidence and a milder degree of cirrhosis; (b) the absence of serous effusions in the peritoneal, pleural and pericardial cavities; (c) better survival rate, and (d) more satisfactory weight curves.

Beneficial effects of thiouracil in these experiments could not be explained by major differences in food intake. The clinical implications of these observations are as

follows: Thiouracil presents itself as a supporting measure in the treatment of cirrhosis in combination with a diet rich in protein and methionine. The high incidence of toxic manifestations following thiouracil therapy does not preclude its use in cirrhosis, in which any improvement in prognosis represents a distinct advantage. Constant clinical observation, with repeated blood counts, is indispensable.

FRANCIS D. MURPHY.

MCGOWAN, J. M. Dynamics of biliary drainage. *Surgery*, 18: 470 (Oct.) 1945. The author first reviews the various indications for T-tube drainage of the common duct at the time of cholecystectomy. He advises that the T-tube be left in place until (1) the resting intra-biliary pressure falls below 30 mm.; (2) the perfusion pain level (determined by perfusing the common bile duct with saline at increasing pressure) is above 500 mm. of water; (3) Roentgen studies of the duct systems show free flow of the medium through the common duct into the duodenum, with no evidence of stone or pancreatitis; (4) the tube can be clamped off for gradually increasing periods, until it can be left entirely closed for 3 weeks without producing symptoms.

A case is reported in which stricture of the ampulla of Vater caused regurgitation of bile into the pancreatic duct, resulting in pancreatitis. This then led to distention of the common bile duct and cholangitis. The resulting chills and fever were similar to those caused by malaria and led to some confusion in diagnosis.

HENRY TUMEN.

ULCER

MORRISON, L. M. Peptic ulcer disappearance after feedings of normal human gastric juice. *Am. J. Dig. Dis.*, 12: 323 (Oct.) 1945.

This clinician removed the gastric juice from normal subjects and fed this, after suitable preparation, to patients with peptic ulcer. In this way, it was believed, the protective principle in the stomach and duodenal mucosa might be demonstrated. The relief of peptic ulcer symptoms and prompt roentgen disappearance of peptic

ulcer is herein recorded following the feeding of gastric juice from normal human subjects. Evidence is presented which tends to indicate that a "protective principle" is elaborated within the gastric and duodenal mucous membranes and secreted into the gastric juice. This protective principle may be lacking or be impaired in patients with peptic ulcer.

H. J. SIMS.

MORRISON, L. M. The prevention of induced peptic ulcer in dogs by feeding a hog stomach preparation. *Am. J. Dig. Dis.*, 12: 328 (Oct.) 1945.

A series of dogs were fed yellow cinchophen by which peptic ulceration developed. In another group of dogs, yellow cinchophen was fed in the same way, but in addition, they were fed a mucosal and submucosal preparation from the hog's stomach and duodenum. These dogs did not develop peptic ulcers. It is the opinion of the author that a "protective principle" is elaborated by the human mucosa, and that this protects the stomach from self-digestion and ulcer formation."

H. J. SIMS.

SURGERY

LEVY, S. An aid in the post-operative management of temporary ileal fistula after the Lahey right hemicolectomy. *Brit. J. Surg.*, 33: 160 (Oct.) 1945.

Right hemicolectomy, using the Lahey modification of the Paul-Mikulicz plan of operation, is associated with a significantly low mortality-rate; it can be performed in the presence of obstruction without prior decompression, and is not a difficult operation. The chief disadvantage of this operation arises from the effects of the ileal contents discharging on to the skin and into the dressings for several weeks.

These disadvantages are overcome by the use of the ileostomy pan, which, by automatically diverting the ileal stream away from the fistula without leakage on to the skin or into dressings, prevents skin excoriation, avoids the necessity for copious and frequent dressings, and thus enables the patient to get adequate mental and physical rest. Furthermore, more reliable fixation of the enterotome is obtained by this method

than with gauze and wool dressings alone. Lastly, but not least in importance, the use of the pan drastically spares the exertions of the nursing staff.

FRAZ J. LUST

SHALLOW, T. A., EGER, S. A. AND TOURISH, W. J. An improved method for extra-peritoneal closure of colostomy. *Surgery*, 18: 466 (Oct.) 1945.

The authors describe a technique for extra-peritoneal closure of a colostomy. The essential feature is the utilization of a fascial rim of external rectus sheath as an extra layer on the closure. This affords additional support to the suture lines and minimizes complications. Of 75 colostomy cases in which this technique was used, primary healing occurred in 61. In only 2 cases was it necessary to do a secondary spur crush.

HENRY TUMEN.

PATHOLOGY

COX, A. J., JR. AND BARNES, V. R. Experimental hyperplasia of the stomach mucosa. *Proc. Soc. Exp. Biol. Med.*, 60: 118 (Oct.) 1945.

The authors have investigated the possibility that stomachs with large numbers of secreting cells may be instances of hyperplasia associated with increased functional activity. An attempt was made to produce hyperplasia of the acid secretory cells in the stomachs of guinea pigs by prolonged stimulation with injected histamine, according to the method of Code and Varco. The results were evaluated by histological methods.

An increase in the number of parietal cells occurred in the mucosa after protracted stimulation with histamine over a period of 2 to 4 weeks. This is presumably a hyperplasia and may explain differences in the number of secreting cells in different human stomachs.

H. NECHELES.

DUNN, T. B. Paneth cells in carcinomas of the small intestine in a mouse and in a rat. *J. Natl. Cancer Inst.*, 6: 113 (Oct.) 1945.

Carcinomas of the small intestine are rare tumors in laboratory animals. The authors have had an opportunity to study 2 induced tumors at this site, one in a mouse and one

in a rat. The carcinoma in the mouse developed in a strain A backcross, aged 18½ months, that had received a methylcholanthrene-olive oil emulsion with acid pepsin in the drinking water for 13 months. Lung tumors, multiple papillomas of the fore-stomach, and atrophy of the testicle were also found.

The Paneth cells were most abundant in the basal portions of the neoplastic glands. By maintaining this location, similar to that of the normal intestinal gland, the tumor suggests an organ reproduction rather than a single-cell reproduction. The Paneth cells in the neoplastic mucosa were interspersed with cells resembling the common epithelial cells and occasional goblet cells. One such tumor has been successfully transplanted and has been carried for 5 years; no Paneth cells are present in the transplant.

The carcinoma of the rat occurred in a 14-month-old male of the Buffalo strain which received N-acetyl-2-aminofluorene in the diet. The tumor had extended into the mesentery and pancreatic tissue. It was in the infiltration into the pancreas that a few Paneth cells were observed. Opinions on the nature of the Paneth cell are divided. Some believe that the Paneth cells give evidence of being mucoid in character rather than independent zymogenic cells, while others believe that they are secretory zymogenic cells, entirely different from the argen-taffin cells.

H. NECHELES

PUGH, D. G., KVALE, W. F. AND MARGULIES, H. Scleroderma with involvement of the viscera: Report of a case. Proc. Staff Meet. Mayo Clinic, 20: 410 (Oct.) 1945. Visceral involvement due to scleroderma may occur along with cutaneous manifestations of this disease. Lungs and gastro-intestinal tract may be affected, as shown by X-ray examination. Myocardial involvement may even be shown clinically. The lesions of scleroderma seem to result from an abnormal change in collagen; edema of the connective tissue is followed by infiltration of lymphocytes and mononuclear leukocytes. The edema and cellular infiltration disappear as the lesions progress, and a disturbance of the colloidal collagen predominates. The collagen fibers become enor-

mously thickened and new collagen fibers are formed; at the same time degeneration and fragmentation of the elastic fibers and muscles take place. The proliferation and alteration of the collagen fibers accounts for the induration of the tissues.

A forty year old male had scleroderma of the hands, back, thorax, scrotum, etc., for several years. The patient had a recurrent duodenal ulcer of 18 years' duration. Chest plate revealed pulmonary fibrosis. A year and a half later cutaneous involvement was more marked and roentgenologic examination revealed changes in the esophagus and terminal ileum — an induration and stiffening of the wall with an impairment of normal peristalsis. The esophagus appeared as a stiff open tube with no power of contractility at all. Dyspnoea and electrocardiographic changes may have represented myocardial involvement by the scleroderma.

FRANK NEUWELT.

PHYSIOLOGY: ABSORPTION

VISSCHER, M. B. AND ROEPKE, R. R. Influence of induced changes in blood plasma osmotic activity on intestinal absorption. Proc. Soc. Exp. Biol. Med., 60: 1 (Oct.) 1945.

Since isotonic salt solutions become hypotonic within a short time after introduction into ileal segments in dogs, it was of interest to ascertain the effect of altering the osmotic activity of the blood plasma upon the degree of hypotonicity so developed.

Adjacent ileal segments were prepared in nembutalized dogs, and measured volumes of isotonic solutions of equiosmotic proportions of sodium chloride and sodium sulfate were introduced. The osmotic activity of originally isotonic sodium chloride-sodium sulfate solutions placed in the ileum rises above the pre-injection plasma osmotic activity after 100 cc. of 5% sodium chloride solution was injected intravenously.

These data add to previous evidence that, although normal osmotic forces are probably contributing factors in the transport of water across the intestinal epithelium, they are not the primary driving forces determining the direction and magnitude of net water transfer.

H. NECHELES

PHYSIOLOGY: SECRETION

UVNAS, B. The presence of a gastric secretory excitant in the human gastric and duodenal mucosa. *Acta Physiol. Scand.*, 10: 97 (Sept.) 1945.

The existence of a protein-like secretory excitant in the pyloric mucosa of cats, dogs, and pigs has previously been reported. The agent was assumed to be identical with the gastric hormone. Since an investigation of the distribution of this secretory principle in the human stomach might throw some light on the hormonal control of gastric secretion, the author studied the gastric mucosa of some surgical cases for its content of the secretory agent. In addition, he investigated the secretory activity of some preparations from human post-mortem gastric and duodenal mucosa.

The pyloric mucosa from 4 cases of duodenal ulcer, 5 cases of gastric ulcer, and 1 case of malignant gastric ulcer was examined for its content of a gastric secretory agent. All preparations except one caused a marked secretion. In 2 cases of gastric carcinoma, one preparation was active, the other inactive. On the other hand practically no activity was observed in the preparations from the corpus mucosa. The post-mortem pyloric mucosa from 24 patients suffering from different diseases was examined in the same way. Six preparations were inactive and 4 slightly active, while the remaining 14 evoked a marked gastric secretion. Five preparations from the corpus were all inactive. Out of 15 duodenal preparations, 9 were inactive, 3 showed an insignificant activity and only 3 were slightly but distinctly active. The investigated surgical material is rather small, but it definitely shows that the human gastric mucosa of the pylorus contains a protein-like secretory principle. The principle is not identical with the "gastrin" obtained from post-mortem and duodenal mucosa by Ivy and others. The "gastrin" and "gastrin bodies" are histamine or some related imidazol derivatives. The principle described in this report is protein-like and is probably identical with the true gastric hormone, gastrin.

ALBERT CORNELL

SCHONHEYDER, F. AND VOLQVARTZ, K. On the activation of pancreatic lipase by cal-

cium chloride at varying pH. *Acta Physiol. Scand.*, 10: 62 (Aug.) 1945.

In spite of an extensive literature on lipases, several elementary questions concerning these enzymes have not yet been satisfactorily answered. In the present paper the influence of calcium chloride on the activity of pancreatic lipase is investigated.

The activating influence of calcium chloride on the hydrolysis by this lipase of several saturated triglycerides and triolein has been studied at different pH levels. With an increasing number of carbon atoms in the fatty acids of the triglycerides, the optimum pH for pancreatic lipase is displaced from 7 to 8.8. Addition of calcium chloride does not alter the optimum pH for the enzymatic activity towards any one triglyceride. Calcium chloride activates the hydrolysis of all triglycerides investigated in homogeneous as well as in heterogeneous systems; also, both in alkaline and acid medium.

In the presence of calcium chloride, the pH activity range for the higher saturated triglycerides is widened one pH unit on the acid side. The higher free fatty acids are supposed to depress the hydrolysis by pancreatic lipase in a high degree and the pronounced activation by calcium chloride in experiments with higher triglycerides is explained by the removal of free acids as insoluble calcium soaps. The experiments do not support Willstätter's theory of the activation of lipase by formation of complex adsorbates.

ALBERT CORNELL.

KAULBERSZ, J., PATTERSON, T. L., SANDWEISS, D. J. AND SALTZSTEIN, H. C. The relation of endocrine glands to the gastric secretory depressant in urine (urogastrone). *Science*, 102: 530 (Nov.) 1945. This work is part of a systematic investigation of the effect of certain endocrine glands on the production of urogastrone, a gastric secretory depressant in urine. Three of these glands—thyroids, ovaries, and pituitaries—have been removed to date from different series of dogs, and collections of urine have been made from these animals.

Preliminary data indicate a relationship between the pituitary gland and gastric secretion. When the gland is removed, the dog's urine contains very little, if any, of the gastric secretory depressant. In addition,

when its urine extract is administered to Heidenhain or fistula dogs, an increase in the quantity of gastric juice is noted. This may suggest that, with a disturbance in the pituitary gland, factors which augment the action of gastric secretory stimulants come into greater play, and contribute to ulcer formation. Further work is in progress.

FRANCIS D. MURPHY.

METABOLISM AND NUTRITION

SCOTT, W. J. M. Idiopathic dilatation of the esophagus. *Ann. Surg.*, 122: 582 (Oct.) 1945.

Scott reviews 85 instances of idiopathic dilatation of the esophagus and suggests a classification into 4 clinical types: (1) achalasia of the cardia, (2) cardiospasm, (3) constriction at the lower end of the esophagus, and (4) dolichoesophagus (extreme increase in length of the esophagus). Types 3 and 4 are infrequent. Cardiospasm is distinguished from achalasia by the finding of a "reflex focus of irritation" (usually peptic ulcer of the stomach or duodenum).

In the majority of cases instrumental dilatation of the cardia affords symptomatic relief. Rarely, such manipulation gives either no relief or transient and inadequate relief from dysphagia. Gastro-esophagostomy has been reported in 21 such intractable cases. Scott adds 3 additional cases of subdiaphragmatic gastro-esophagostomy with good results in each.

LEMUEL C. McGEE.

PHARMACOLOGY

CHU, W. C., FIESE, M. J., CUTTING, W. C. AND COLLEN, M. F. Absorption of penicillin from the nose and alimentary canal. *Proc. Soc. Exp. Biol. Med.*, 60: 159 (Oct.) 1945.

The relative absorption of penicillin by various routes in man and animals are compared. Sodium-penicillin was used apparently, although this is not stated. Assays were made by the method of Wolohan and Cutting on whole blood.

Penicillin is absorbed from the esophagus, stomach, duodenum, ileum, or colon of rats about one-fifth as well as from intramuscular injection. Penicillin is also absorbed from the nose and mouth of dogs, about one-fourth as well as from intramuscular injec-

tion. Concentrations higher than 25,000 units of penicillin per cc. depress the ciliary activity in frog's esophagus. Penicillin may be sprayed into the nose in concentrations of 100,000 units per cc. without producing significant irritation. Although the blood concentrations following intranasal spraying of penicillin are low, they may enhance local antibacterial effects in the upper respiratory tract.

H. NECHELES.

MISCELLANEOUS

YATES, J. Acid-fast organisms in gastric resting juice. *Brit. Med. J.*, 4424: 530 (Oct.) 1945.

In 171 specimens of resting gastric juice examined for acid-fast organisms from patients not suspected of suffering from tuberculosis, 7 were found with acid-fast organisms. They were mostly of a short stout shape, unlike true tubercle bacilli. On culture, 3 of the 7 specimens gave a growth of saprophytic acid-fast organisms. All 7 specimens on guinea pig inoculation had failed to produce any lesions. These organisms were also alcohol-fast and this finding is not sufficient to identify it conclusively as the tubercle bacillus. The author concludes that under normal conditions the chance of tubercle bacilli being found in gastric resting juice of non-tuberculous patients is very remote.

MAURICE FELDMAN.

ROSTORFER, H. H. AND LASKOWSKI, M. Action of histaminase preparations in the Heidenhain dog. *Am. J. Dig. Dis.*, 12: 337 (Oct.) 1945.

These investigators made an experimental study of the action of histaminase in dogs. Preparations of histaminase from hog kidney, having potencies of at least one unit per mg. of protein, were found to be highly toxic when injected intravenously into dogs in amounts above 300 mg. The toxicity apparently was not due to histaminase itself, because a preparation of histaminase which had been inactivated was found to be even more toxic per mg. of protein. The toxic symptoms observed were trembling of extremities, coldness, ischemia of the gastric mucosa, vomiting, and defecation.

H. J. SIMS.



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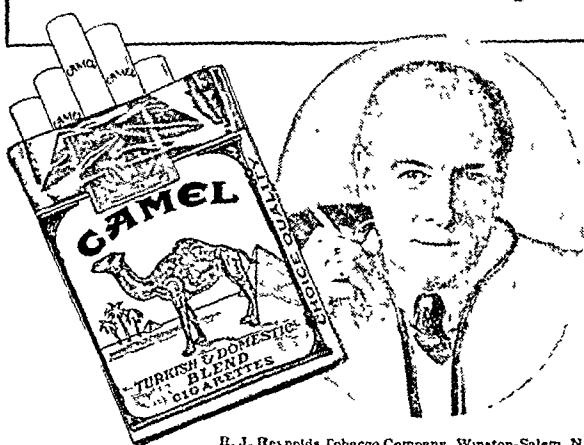
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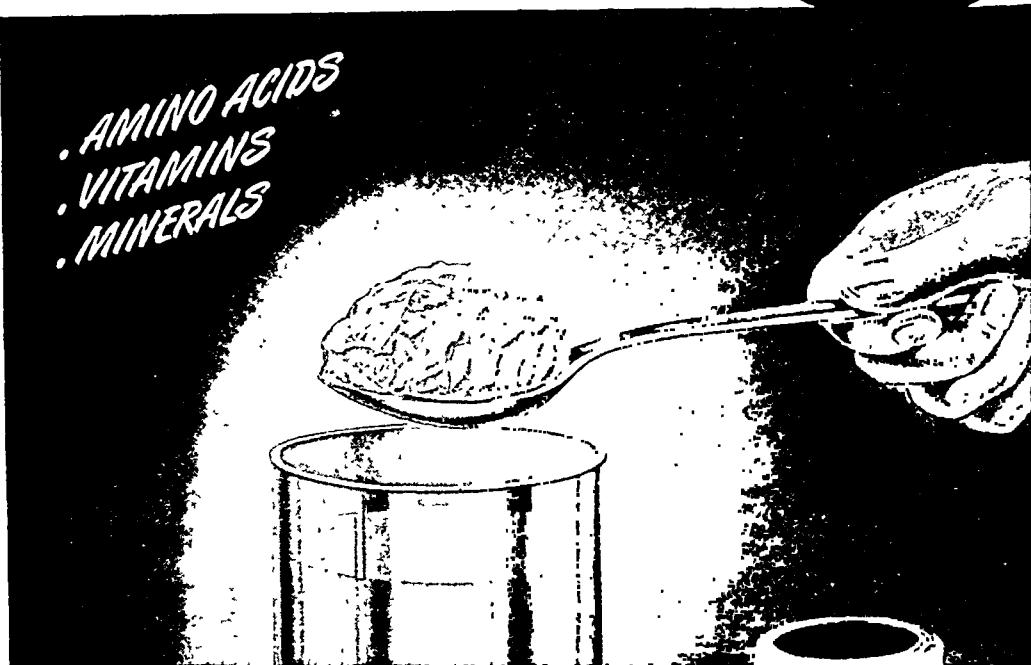
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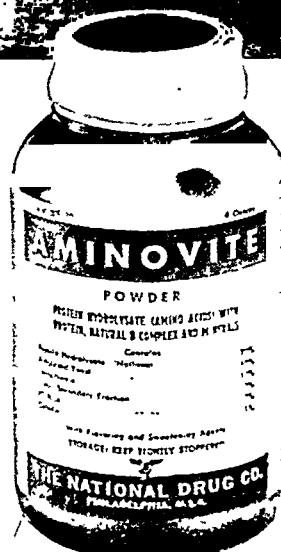
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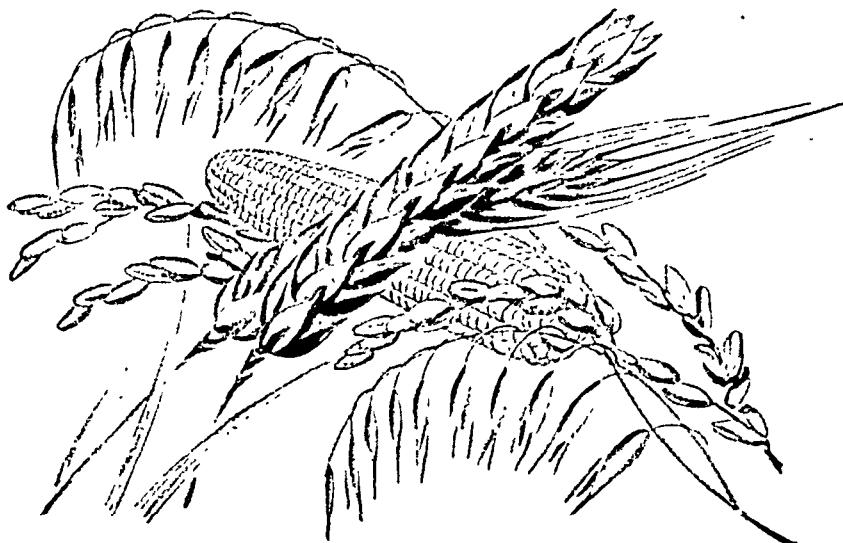
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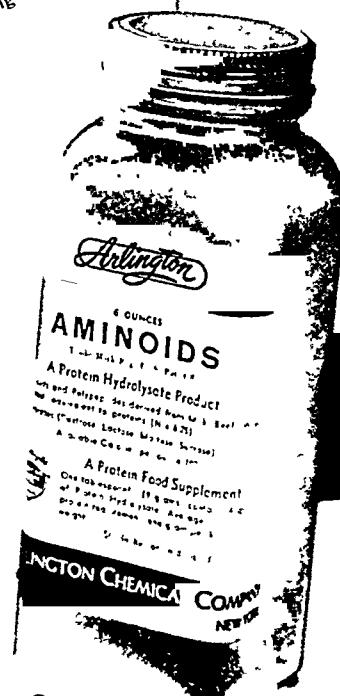
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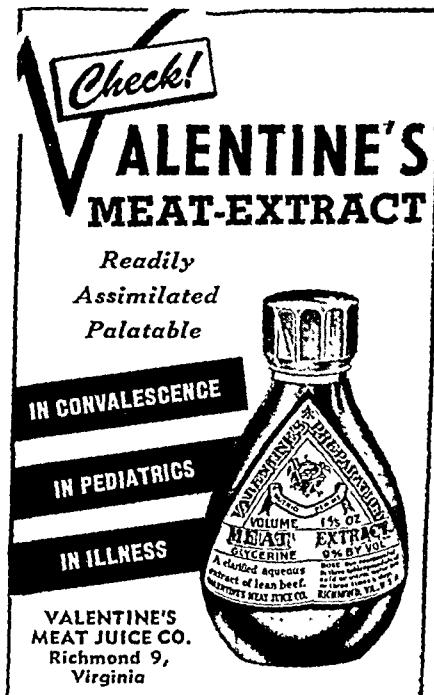
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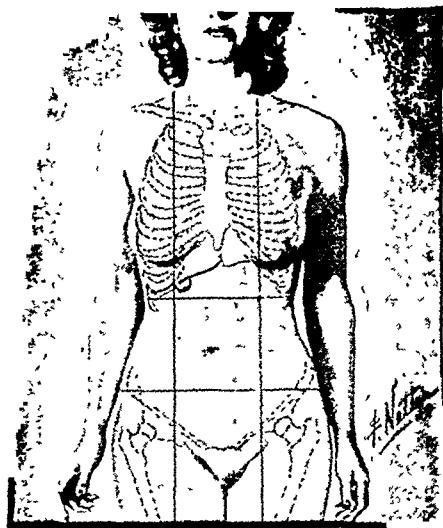
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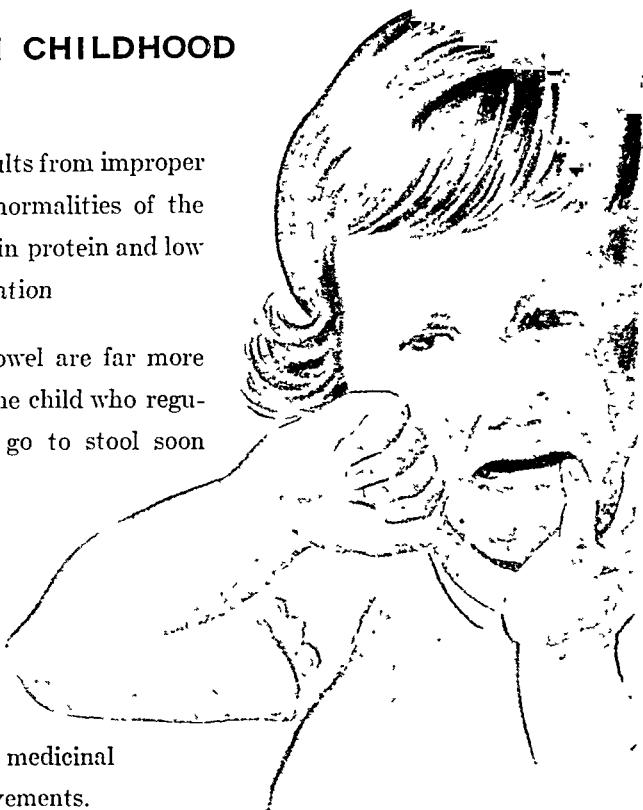
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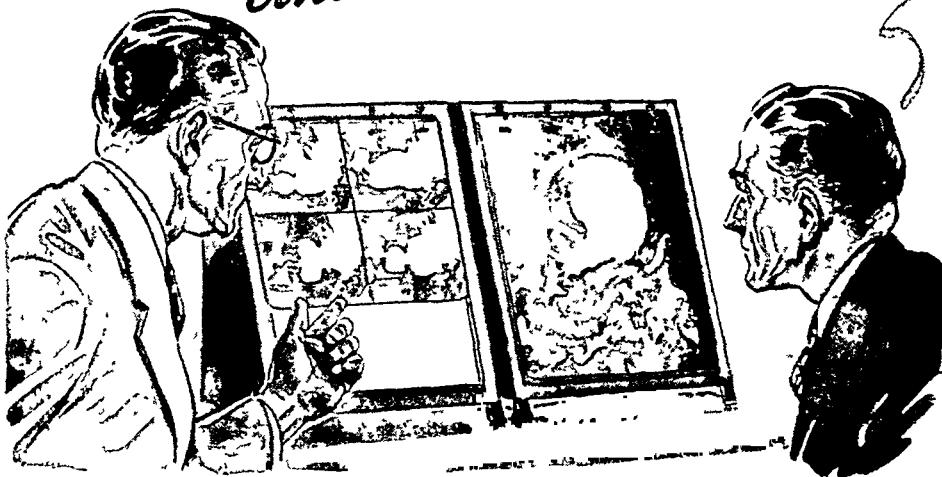
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INDEX TO ADVERTISERS

	PAGE
Abbott Laboratories.....	Cover 3
Arlington Chemical Co.....	23
Armour Laboratories.....	25
Burnham Soluble Iodine Co.....	26
Burroughs Wellcome & Co.....	6
Burton, Parsons & Co.....	24
Camel Cigarettes.....	18
Cereal Institute, Inc.....	20
Ciba Pharmaceutical Prod., Inc.	8
Harrower Laboratory.....	14
Hoffmann-LaRoche, Inc.....	32
Knox Gelatine.....	31
Lilly, Eli, & Co.....	16
Maltbie Chemical Co.....	11
Massengill Company, S. E.....	13
Mead Johnson & Company.....	1
Merck & Company, Inc.....	5
Merrell Co., William S.....	12
National Drug Co.....	19
Parke, Davis & Company.....	15
Patch, E. L., Co.....	27
Paxton, F. H., & Sons, Inc.....	24
Riedel-de Haen, Inc.....	2
Schering Corp.....	13
Searle & Company, G. D.....	17
Stearns & Co., Frederick.....	9
Valentine's Meat-Juice Co.....	24
Warner & Co., Inc., Wm. R.....	7
Wander Company	21
Welin-Sater Co.....	24
Winthrop Chemical Co., Inc. 12, Cover 4	
Wyeth, John & Brother, Inc...Cover 2	



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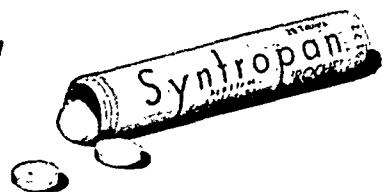
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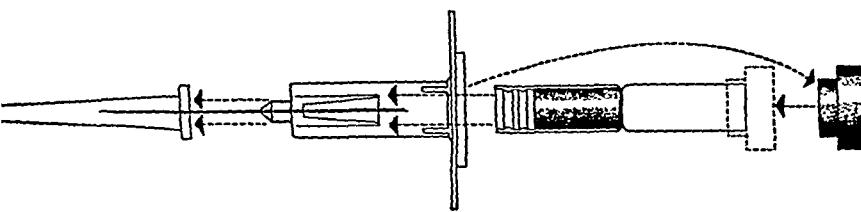
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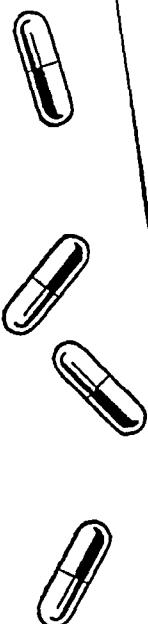
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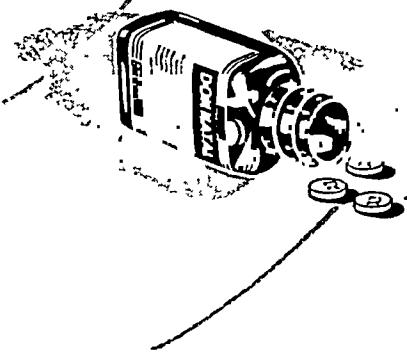
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GASTROENTEROLOGY

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TABLE OF CONTENTS

The President's Address. A. H. AARON.	153
Military Gastroenterology—The summing-up. DONALD T. CHAMBERLIN, M.D.	162
The Differential Diagnosis of 207 Hospitalized Cases of Peptic Ulcer. ROBERT C. KIRK, M.D.	168
Correlated Gastroscopic and Psychiatric Studies of Soldiers with Chronic Non-Ulcerative Dyspepsia. JAMES A. HALSTED, M.D., I. RICHARD SCHWARTZ, M.D., SAMUEL R. ROSEN, M.D., HENRY WEINBERG, AND STANLEY M. WYMAN, M.D.	177
Clinical Findings in American Soldiers Released from a German Prison Camp. MANFRED KRAEMER, M.D.	191
Gastrointestinal Bleeding in Hereditary Hemorrhagic Telangiectasia Historical Review and Case Report with Gastroscopic Findings and Rutin Therapy. SAMUEL D. KUSHLAN, M.D.	199
The Effects of B-Dimethylaminoethyl Benzilate Hydrochloride on Intestinal Activity. K. G. WAKIM, M.D., PH.D., CLARENCE E. POWELL, B.A., AND K. K. CHEN, PH.D., M.D.	213
The Effect of Glucose on the Motility of the Stomach and Small Intestine. EDWARD J. VANLIERE, PH.D., M.D., DAVID W. NORTHUP, PH.D., AND J. CLIFFORD STICKNEY, PH.D.	218
The Effect of Pilocarpine on Mucus Secretion by the Pyloric Mucosa J. S. IVY, M.S., M.D.	224

CLINICAL PATHOLOGICAL CONFERENCES AND INSTRUCTIVE CASES

Hematemesis Associated with Gastric Arteriosclerosis; a Review of the Literature with a Case Report. WILLIAM FRANK, M.D.	231
Puzzling "Nervous Storms" Due to Food Allergy. WALTER C. ALVAREZ, M.D.	241
Clinical Pathological Conference. A. J. ATKINSON, M.S., M.D.	243

EDITORIALS

Dr. Aaron's Presidential Address. W. C. A.	249
The Use of Elimination Diets and Food Diaries in the Diagnosis of Food Allergy. W. C. A.	249
Gastric Tumors Produced in Insects by Cutting the Nerve to the Stomach W. C. A.	252

(Continued on p. 4)

For Instructions to Authors and the address of the Editor see the advertising section following the Abstracts.

TABLE OF CONTENTS—CONTINUED

COMMENT

Supradiaphragmatic Vagotomy for Ulcer. H. M. POLLARD, WILLIAM H. BACHRACH, AND MALCOLM BLOCK.....	254
Recent Advances in Cytochemistry. PAUL KLEMPERER.....	256
Books—War Victims. K. R. SHAFFER.....	259
Report of Advisory Committee on Gastroenterology of the American Board of Internal Medicine.....	261

BOOK REVIEWS

Gastroenterology.....	264
Medical Diagnosis.....	264
The Person in the Body.....	265

OBITUARIES

Clement R. Jones.....	267
Alexander Berkeley Moore.....	268

ABSTRACTS..... 270

ANNOUNCEMENTS

American Board of Internal Medicine

The next written examination of this Board will be held on October 21, 1946. The closing date for acceptance of applications for this examination will be July 1, 1946. For particulars address Dr. William A. Werrell, One West Main Street, Madison, Wisconsin.

Information Regarding Post-Graduate Instruction in Gastroenterology

At the request of the Board of Governors of the American Gastroenterological Association, Dr. Julian M. Ruffin wrote the members of the Association to ascertain those members and institutions which were able to provide a short course or extended graduate study in Gastroenterology. The following have responded.

Those who are interested in obtaining such instruction should write promptly to the person or school of their choice, because in most instances the number of students who can be accommodated is limited.

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1. Holling, H. E.; McArdle, B., and Trotter, W.R.: Lancet 1:127, 1944.
2. Hill, I. G. W., and Guest, A. I.: Brit. M. J. 2:6, 1945.
3. A Critical Study of Seasickness Remedies, No. 4, Royal Naval Medical Bulletin 24:3, 1943, abstracted, Bulletin of War Medicine 18:1242, 1945.
4. Lillienthal, J. L.: J. Aviation Med. 16:59, 1945.

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VOLUME 7, NUMBER 1

GASTROENTEROLOGY*Official Journal of the American Gastroenterological Association*WALTER C. ALVAREZ, *Editor*A. C. IVY, *Assistant Editor*

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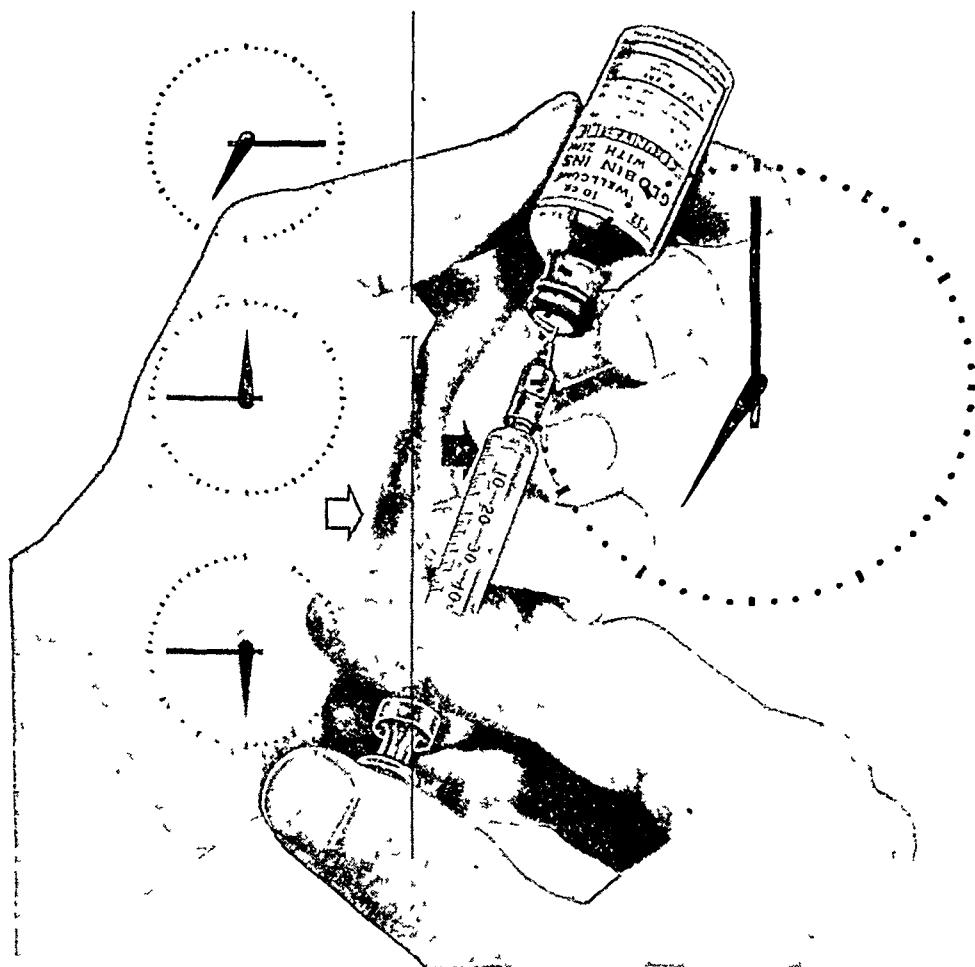


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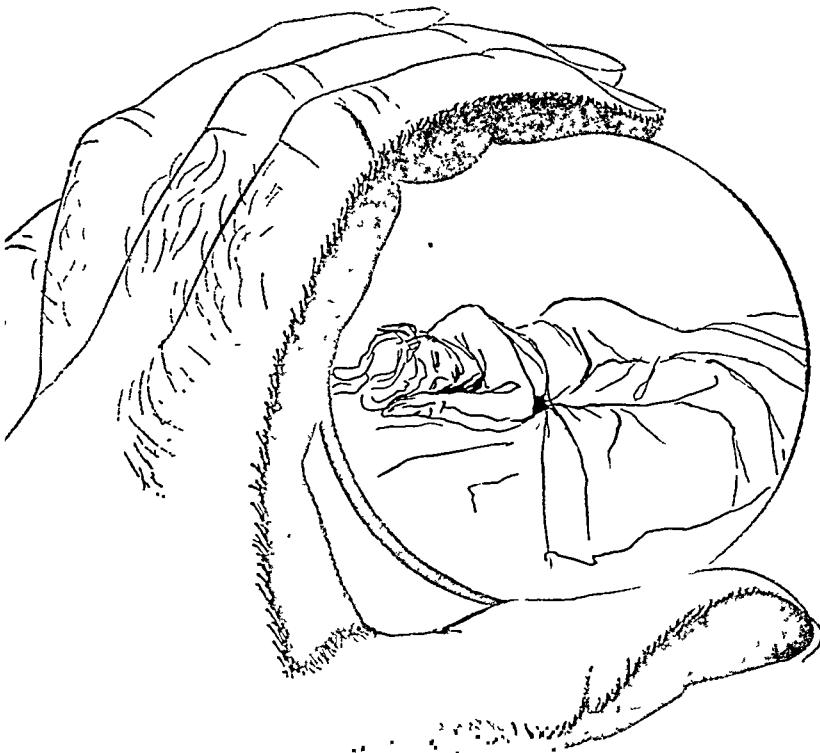
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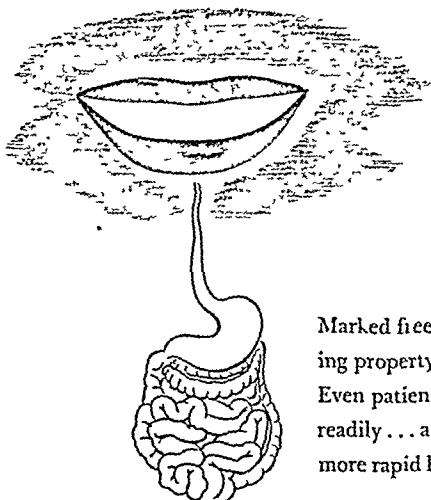
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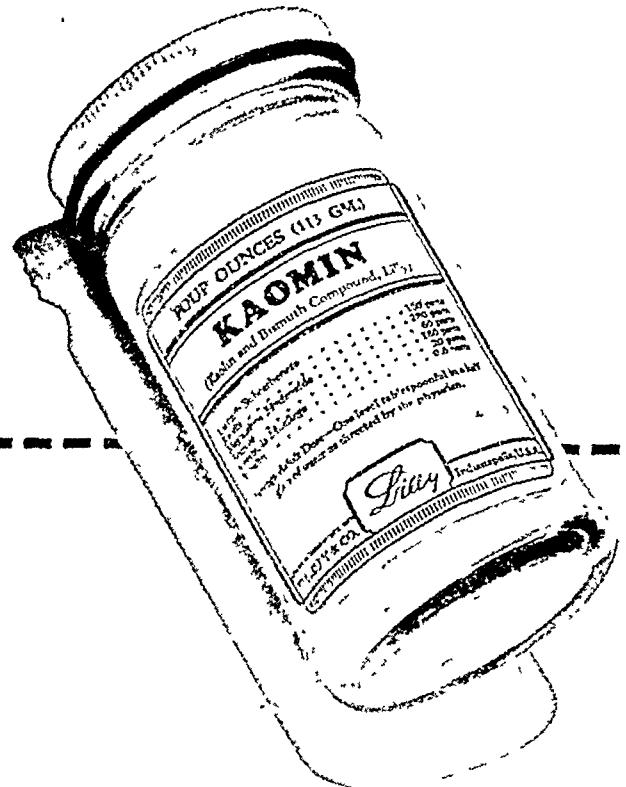
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*Remikoff, P., and Goebel, W. F., J. Clin. Investigation 16:547, 1937

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GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

VOLUME 7

August 1946

NUMBER 2

THE PRESIDENT'S ADDRESS

A. H. AARON, M.D.

Buffalo, New York

For the first time in four years the entire membership of this Society meets within the security of our great nation. It is with a sense of unequalness to the task of expressing in words the momentousness of this occasion that I now present the Annual Address of the President. Because of the War, I, like my predecessor, have had the honor of being continued in this office for a period of two years. At this time I welcome you to the Forty Seventh Annual Scientific Meeting of the American Gastroenterological Association.

It is fitting that I should open this address with a word of tribute to those members who have given up from one to five years of the most productive period of their lives to the service of their country. This Society cannot sufficiently honor these men for their sacrifices, but we can now apply to private practice the methods and special skills which they developed during the war, with such spectacular results. In this way we can acknowledge their great accomplishments.

With the opening of the conflict and during the period of warfare, the past officers of this association, in cooperation with the Surgeons-General of the Army, Navy and Public Health, aided in the establishment of the divisions of Gastroenterology in the several medical units. The wisdom of this becomes evident when one realizes how high was the incidence of diseases of the gastrointestinal tract in this war.

Our members in the armed forces demonstrated the value of their particular training which made for a more rapid and complete diagnosis and better therapy in caring for the sick, and resulted in a shortening of the period of hospitalization of the soldier, and his more rapid return to duty. It is due to the excellent quality of these services that the specialty of Gastroenterology was brought into high repute and that the years of effort of the members of this Association to establish and maintain through the specialty sub-boards the outstanding position of Gastroenterology in Internal Medicine have been rewarded.

The wide variety of gastrointestinal lesions our members were called upon to treat, demonstrates how necessary it is that in the future we avoid limiting our

training to a small group of diseases; we must all be physicians and internists as well as "specialists."

The members of the Association who remained at home served on various Selective Service Boards and Induction Teams, assumed additional teaching responsibilities, and conducted special postgraduate clinics for the medical personnel of the armed forces in this country, and in addition carried the tremendous burden of caring for the civilian sick.

Because of the war we have had only two meetings of the Association in the past four years, consequently many of our members in the armed forces have not had ready access to our official publication or opportunity to attend our scientific meetings. As there is no provision for conveying information to the membership at the Annual Business Meeting, I will in this address give you a brief summary of our activities during the past two years, and will make suggestions regarding our responsibilities to the future of the Association.

Like other officers who have preceded me I have carefully consulted the previous presidential addresses, and I find them filled with excellent advice, fundamental concepts and stimulating thoughts. In 1904, forty-two years ago, Simon J. Meltzer in his presidential address said:

I would like also to go on record with another suggestion, which to my mind would tend to solidify and elevate our Association. It is to start an American Journal (monthly or quarterly) for gastroenterology, under the careful editorial management of this Association. The original articles should not be too many and only of the first order. But the Journal should contain a complete classified account of the gastro-enterological literature of this country. However, this suggestion is not offered for its immediate consideration. Elevation, growth and development of our Association should be for the present our first and sole task.

In the past three years our Association has established on a firm footing what has now become the outstanding journal on diseases of the gastrointestinal tract. Its Editorial Board, by careful selection, has set and maintains the standard for the publication of scientific material. By this the reader is assured that what appears is authoritative in its quality, character and thought. Our Journal is a required periodical on the shelves of all libraries in hospitals and teaching institutions.

I feel certain that the membership is not well acquainted with another phase of the activities of the Editorial Council. All advertising material appearing in our Journal is carefully investigated by individuals capable of appraising the statements and claims. In evaluating a pharmaceutical product we use information derived not only from investigative and laboratory groups, but also from clinicians who have been asked to consider the results of its application in the treatment of disease. I doubt if, until now, the membership have known of these methods of your advertising council.

I should like now to call your attention to some of our problems. An advertisement was recently submitted on the value of certain protein hydrolysates. The statements and claims were sent to a member of our society who has contributed much to the present day knowledge in regard to these products, and he answered as follows:

I do not approve of it any more than I would approve of an advertisement for insulin in which the physiological activity of the material was unknown. It seems to me that any preparation, whether given by mouth or parenterally, should first be shown to be physiologically adequate. For example—I know that several tests carried on with this product proved that it did not contain a complete mixture of the essential amino acids and was therefore ineffective as a source of nitrogen nutrition. Subsequently, this deficiency was apparently made up. The present preparation may be quite adequate. No statement is made as to any tests having been carried out, and in the absence thereof I would certainly not recommend it for any of my patients, and feel that we might be seriously criticized if we permitted an advertisement of it to appear in Gastroenterology unless this evidence had been obtained and recorded.

This information has been forwarded to the manufacturing concern, and we now await their response to this criticism.

As a second illustration, a product was suggested for use in the treatment of anemia. On submission to our members and to outside authorities the following was reported:

Frankly I cannot find out whether it is toxic or not, according to the literature I have. The chart is poor, unhelpful and misleading. Even liver extract received scientific publication before it was advertised. If you are attempting to keep the advertising in your Journal at a high level, I believe you would be justified in demanding more information.

The firm interested in this product, at our request, furnished additional information for the individuals who had originally studied the advertisement, resulting in a reconsideration and our acceptance as follows:

If our policy is to accept advertising of a relatively safe, ethical and effective product, I can see no objection to this one.

In this case the Association has helped the manufacturing firm in preparing their claims, and in establishing the accuracy of their conclusions.

In the complex field of biliary tract drugs we have helped to eliminate much of the confusion that existed as to whether an agent increased the output of bile, or affected its watery content, or increased the output of bile acids and their salts, or acted as a gallbladder evacuant. The advertising council of "Gastroenterology" has carefully studied the claims made for various products

and has aided in the organization of the data and in deciding on the manner of their presentation; and it has clarified the claims of the companies in regard to the various products used in the treatment of biliary tract disease. We have called the attention of the manufacturer to the wisdom of including in their advertising pages references to the original publications which substantiate the statements made, and this valuable idea is now being extensively adopted.

The elimination of all products which do not meet these high standards places our advertising pages in a premier class. In this manner your journal and its advertising council serve to establish and set a seal of approval upon products appearing in its pages. This is of vital importance in establishing the value of drugs whose principal action is on the digestive tract. A product will frequently be under consideration for some time before it is accepted or rejected. By this means the advertising pages of our journal are kept free from claims that cannot be substantiated clinically or in the laboratory.

This attitude has met with the excellent cooperation on the part of the manufacturers utilizing our journal. To the medical profession at large this screening is of great value. Our approval of a pharmaceutical product brings a distinction of merit. The success of the journal has not been built up upon the acceptance of advertising that does not meet the rigid standards we have established. Again the Association is fortunate in possessing within its ranks individuals whose training qualifies them to make decisions in these important matters. We are indebted to other outside authorities for opinions freely given.

The present success of the Journal calls for an increased number of clinical and scientific papers, editorial contributions and comments, and I am sure that these will be forthcoming now that a greater number of our members have returned from the Armed Forces, resulting in an improvement of all of our schedules.

I doubt if we should train specialists in any division of undergraduate teaching. We gastroenterologists must fit ourselves into the whole of internal medicine. Nevertheless, I feel that we are justified in requesting of University Deans adequate time in which to teach the facts in regard to certain fundamental diseases of the digestive tract. This teaching must bring out the alterations of anatomical structure and physiological function produced by the diseases.

We must not confine our teaching entirely to diseases of adults or of a limited group of conditions. In the past I fear we have unintentionally avoided a discussion and presentation of the manifestations of gastrointestinal disease in younger children and the teen age group. Similarly, because of the present day prolongation of life, it becomes important that we consider and teach digestive troubles as they occur in the older age groups.

The return to civilian life of thousands of individuals who have had parasitic infestation of the gastrointestinal tract will require greater efforts at teaching the manifestations of these diseases, and the ways in which they bring about lesions of the digestive tract and the blood forming organs. The importance of this is indicated by the fact that in the past two months in our Buffalo teaching hospitals, our medical service has been confronted with nineteen cases of malaria, two of the acute fulminating cerebral type, several cases of amebiasis, and one of Kala Azar with its multitude of clinical manifestations.

In undergraduate teaching there should be a radical change in history taking. Emphasis should be placed upon the different areas of the United States and world where patients have lived and traveled. The universal administration of typhoid prevention inoculations must be considered, the gastrointestinal manifestations of malaria thoroughly taught, the complications of amebiasis and other tropical diseases presented. It is clear that the recognition of carriers of tropical disease is now of great importance. It will be necessary for us to assume a more positive attitude in preventive medicine in relation to lesions of the gastrointestinal tract. It is possible that the repeated bouts of peptic ulcer may be reduced by adequate therapy inaugurated at times of anticipated stress or strain. The foundation for a comprehension of the psychiatric phase of symptom complexes of the digestive system must be emphasized in the undergraduate training.

These are not the functions of graduate teaching alone, and the quality of gastroenterology of the future will have to be created on a firm foundation provided for in the time allocated for a course in general medicine in the junior and senior years. Our own particular training in this field calls for a utilization of these talents by all teaching institutions.

The demands placed upon our personnel in the Armed Forces and their resulting success has demonstrated the value of the trained individual in the gastrointestinal field of internal medicine. With the establishment of the boards of internal medicine and the sub-specialties, and with a greater number of young physicians seeking this certification, it becomes necessary for all of us to participate in a training program. Your Association has set up a plan, and an opportunity for such a program can be made available only if every member of the Association will assume as his personal responsibility the obligation to associate with him in his clinic or practice or hospital service young men and women who want to secure this training. This is necessary if these young physicians are ever to become eligible for examination and certification. We cannot depend only on postgraduate schools or large clinics to accomplish this purpose. I should like to recommend to the individual members the advisability of a return to the preceptorial method of teaching.

To stimulate further interest in gastroenterology your Association has established a limited number of fellowships available to qualified individuals

for prolonged investigative periods under suitable supervision. Awards have been inaugurated for outstanding clinical and investigative publications of merit appearing in our journal. These activities have been made possible by the funds which have resulted from the success of the journal or have been provided for research.

Our duty in disseminating accurate knowledge of lesions of the gastrointestinal tract to the profession as a whole must not be neglected. I think we should anticipate, and look forward to the establishment of the type of short, refresher courses which at the beginning of the war were given to medical officers in this country.

We must emphasize the value of the work of the practitioner who first sees the patient with gastrointestinal disease at the bedside or in the office, and must remember that their well reported clinical observations are a great help in the advancement of medical science.

The founders of this Association showed great wisdom when they diversified its membership. Few societies possess within their ranks chemists, physiologists, roentgenologists, surgeons, clinicians, nutritionists and parasitologists who can contribute and discuss authoritatively papers with such a wide variety of subjects. Indeed we are fortunate in the broad concepts laid down by the founding fathers of this Association. It is only proper that we should benefit from this far-sightedness, and consider carefully our attitude towards membership in the American Gastroenterological Association. I am certain it is our desire that every physician who has passed certification boards in Internal Medicine and the sub-specialty of Gastroenterology should be carefully considered as a candidate for associate membership.

I can see no reason why such men should not be granted the privilege of associate membership, and in holding forth the advantages of full membership the Association will serve as an incentive for continued effort. We, in turn, will gain by the presence among us of young men, and from the opportunity to hear and discuss their presentations. By this I do not mean that we should become too large a group so that the intimacy and the opportunity for personal contact should be lost, but I feel certain we could increase our associate membership with benefit to the Association as a whole.

Our purpose should be to see that we have the opportunity for firsthand contact with all interested in the scientific study of the diseases of the digestive tract. Your Admissions Committee has taken forward steps in this matter, and has carefully studied and prepared a report for your consideration of many physicians properly trained in gastroenterology who may be available for membership.

An analysis of our membership reveals that if we consider the present senior membership representing a total of twenty-seven, eighteen reside along the

Eastern Seaboard, four in the Chicago area, three in the Southwest, and two in the Far West. This represents the divisions of the membership during the early period of our growth, with a preponderance of members on the Eastern Seaboard, and this explains why the meetings in the past were all held in this area.

When we analyze the composition of the present active and associate membership, which represents the expansion period of the Association, we find that of a total of one hundred and sixty-five members, the Eastern Seaboard is represented by seventy-six, in the Cleveland-Detroit-Chicago and Rochester, Minnesota area there is a total of fifty-four, in the area west of Rochester, Minnesota, and on the western coast there are seventeen members, and in the Southwest, fourteen. If we combine the membership residing in these areas, we have a total of eighty-five in Cleveland and beyond.

Under these circumstances with approximately equal distribution of the membership east of and west of Cleveland, I think we should seriously consider the necessity of advising the Council that the annual meeting should be held frequently in the Chicago-Cleveland area in fairness to the geographical residency of our membership.

Some years ago this Association formed a special committee from widely separated localities to report on the methods and value of the determination of enzymatic substances in the duodenal contents. The reports and conclusions of this committee were of great advantage to many interested in the problems of pancreatic disease. This was one of the first cooperative efforts that the Association had attempted.

On the suggestion of some of our members, I believe we should consider the establishment of groups to carry out investigative work under the sponsorship of the Association. At this time I desire to quote specifically from a communication received from Dr. David Sandweiss requesting the formation of a national committee of the American Gastroenterological Association for the study of peptic ulcer:

While much can be said in favor of individual initiative in the field of research, one might nevertheless ask: Would not greater progress be made in a shorter period of time by a cooperative, concerted, well-planned program of endeavor? Knowledge by each worker of the problem under investigation in the other laboratories would avoid duplication of studies that later prove negative. Encouraging results suggested in one laboratory might be tested in another laboratory much sooner than would otherwise be possible. Assignment of certain complex phases of a problem to men especially adept and especially trained for the specific work would certainly save time, effort, and money. Exchange of ideas at frequent intervals, especially when encouraging findings become apparent, might result in a much better understanding of the problem and perhaps even a different approach (by the same or

another laboratory) toward its solution. A cooperative group could arrange with one or more of the commercial houses to prepare sufficient quantities of the various extracts for all interested laboratories, thus releasing much needed experienced men for more important problems under investigation. A national committee, especially if it were sponsored by the American Gastroenterological Association, might more easily obtain funds to provide more adequate facilities and more trained personnel where needed.

One can readily recognize the value that would be secured in the prevention of duplication of effort, better utilization of funds, larger amount of available clinical material under research sponsored by the Association as a whole. It would facilitate the solving of some of our problems more thoroughly and in a shorter period of time. The advantages of the application of this program to the problems of chronic non-specific ulcerative colitis, cirrhosis of the liver, and many others that come to our mind would be self-evident.

I feel some doubts as to the wisdom of too completely accepting the psychosomatic theory of the origin of certain diseases such as peptic ulcer and chronic non-specific ulcerative colitis. My reasons for so thinking have been arrived at after conference with members of our general hospital and officers of the Armed Forces. I was impressed by the low incidence of peptic ulcer and chronic non-specific ulcerative colitis in military personnel exposed to the most trying psychiatric situations, and who had no previous history of these diseases. The argument that individuals prone to these diseases were screened out is not true, as shown by the fact of the high incidence of psychiatric problems in our fighting forces.

In private practice I am struck by the large number of functional problems in individuals in whom peptic ulcer or ulcerative colitis is rare. Attention to this situation is beginning, I believe, to appear in the literature where authors are questioning the degree of emphasis placed upon psychosomatic factors in the etiology of these diseases. I feel that a cooperative group studying this problem would result in the accumulation of information of great value to the entire profession.

Discussion of these investigative and clinical problems with different authorities would be stimulating and conducive to cooperative effort of the most satisfactory nature.

Many of the ideas and activities that I have called to your attention are in their infancy and their present success has depended upon your officers, special committees, the editors and editorial council of your Journal. To them we all owe our sincere gratitude that under the stress of recent times they have accomplished so much.

I believe that all of us realize that the future developments in the field of

Internal Medicine as it concerns Gastroenterology will depend upon the activity of the membership of the American Gastroenterological Association. A study of previous presidential addresses reveals that past presidents felt free to make suggestions as to the policy or future conduct of the Association, and it is with their example before me that I have presented certain ideas for your consideration. I believe we should appoint committees to make a study of and promote undergraduate teaching of Gastroenterology, and also to support and increase the efforts of the graduate teachers as contemplated by our present committee. I recommend that we give serious consideration to an increase in our membership and a discussion of the location of our annual meeting. I think also that we should establish cooperative committees for the study of certain problems in Gastroenterology.

In conclusion I would emphasize that our Association occupies a premier position in maintaining and augmenting one of the most important fields of Internal Medicine. We possess the qualified type of membership. It advocates broad principles in the choice of future membership. It possesses a well-established Journal as an outlet for its scientific contributions, and an evaluation of medicinal products. It is accumulating the wherewithal to offer fellowships, scholarships and graduate training. It possesses the friendship and fellowship of one for another that has led to meetings of the greatest personal pleasure as well as intellectual stimulation.

In discharging my duties as President of the American Gastroenterological Association I desire to express my appreciation of the great honor that has been conferred upon me to be your presiding officer. It has been my great privilege to serve you.

At this time it would seem proper to renew our faith in the teachings of the Early American Philosopher, Henry David Thoreau, who wrote as follows:

Give me a hammer and let me feel for the furring. Do not depend upon the putty. Drive a nail home and clinch it so faithfully that you can wake up in the night and think of your work with satisfaction, a work at which you would not be ashamed to invoke the Muse. So will help you God, and so only. Every nail driven should be as another rivet in the machine of the Universe, you carrying on the work.

The life in us is like the water in the river, it may rise this year higher than man has ever known it and flood the parched uplands; even this may be the eventful year.

MILITARY GASTRO-ENTEROLOGY—THE SUMMING UP

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INTRODUCTION

In 1942 I was able to report my experiences in the care of soldiers with digestive disorders during the first year of the war (1). At this time, I shall try to give my final impressions of gastro-enterology as a war-time specialty, however, without statistics, as there was much less leisure to collect them during the later years. In due time, I shall present a five year follow-up on one thousand cases of digestive diseases seen during the first two years of the war and whose records I have preserved.

PRINCIPAL DISEASES

The problems in diagnosis and treatment of digestive diseases in the army were identical with those encountered in civil life with few exceptions. The three conditions which caused the greatest number of days lost were the functional disorders, epidemic diarrheas and peptic ulcer. Carcinoma, cholelithiasis, ulcerative colitis, and the other serious organic disorders of the digestive tract are rarely encountered because of the average age of the group with which we were dealing, and the careful preliminary physical examination that each prospective soldier received.

PEPTIC ULCER AND FUNCTIONAL DISORDERS

Difference between civilian and military life

One notable difference between the soldier and the civilian is that the soldier cannot control his diet as can the civilian. For this reason, individuals who were able to work full time, and who lost a minimum time from work because of a chronic digestive disorder in civil life were unable to tolerate the army diet. This was particularly true of the patient with peptic ulcer, but was true also of the individual with a chronic irritable colon, or other functional disorder.

During the first two years of the war this fact was not appreciated by many, and numerous recruits were accepted for service who lasted only a few months because of their inability to tolerate the army diet. During 1942 the average length of service of patients with peptic ulcer admitted to a large general hospital in the United States was five months (2). This represented a great loss of time and money to the government and to the individual. Later this fact became so apparent that a patient with peptic ulcer was usually separated from the service as soon as was practicable after the diagnosis was made.

Influence of home and foreign duty

During 1941 and 1942, before many troops were overseas and before much combat had occurred, there was considerable speculation as to the influence of combat conditions on the incidence of peptic ulcer. Before leaving the United States the author had the opportunity to treat a number of patients with peptic ulcer evacuated from the Pacific. The impression gained from this experience is that combat, even under extraordinarily difficult conditions encountered in our Far Eastern campaign, does not increase the incidence nor the severity of symptoms of peptic ulcer. The men suffering from this condition had as much difficulty as those under training conditions in the United States, but no more. The occurrence of new ulcers was no greater than could properly be expected in any large group of this age. Experience in the European Theater of Operations bore out this impression. The incidence of peptic ulcer among combat troops was not beyond the expectancy in a like number of civilians. An increase may be seen later in veterans, but at present combat does not seem to have increased the incidence of peptic ulcer. Patients with peptic ulcer in the European Theater of Operations were promptly returned to the United States for separation from the service.

Patients with functional digestive disorders were a constant and serious problem. A functional digestive disorder may be defined for military purposes as a condition which renders an individual unfit for military service because of inability to tolerate the army diet without recurrence of symptoms. The symptoms may vary from an occasional loose stool to the most acute nausea and vomiting, all without evidence of organic disease. This group constituted about one-third of all patients admitted to general hospitals for symptoms related to the digestive tract.

In the United States the types of patients and their signs and symptoms were similar to those seen in civil life. They fell roughly into three categories: First, those with symptoms relating to the colon; second, those whose symptoms simulate peptic ulcer; and third, the group whose symptoms are secondary to a profound underlying psychological defect, psychoneurosis, constitutional inadequacy or one of the psychopathic states. This differentiation may seem trivial or carping to some who consider all functional digestive disease on a psychosomatic basis, but such a consideration leaves out the patients whose symptoms had their onset in a sudden acute infection or episode, and who have never quite recovered. Often these patients are completely relieved of their symptoms with proper treatment and suffer no subsequent recurrence. In the first group, about two thirds may be restored to full duty, in the second group about one half, but in the third group the prognosis is nearly always hopeless as far as a useful army career is concerned (3). The maladjusted indi-

vidual whose failure to adapt is manifested by indigestion has no place in the army.

In the United States, in the large general military hospitals the facilities for diagnosis and treatment of all patients are equal to and in some ways superior to those in civilian hospitals. This made the care and treatment of military personnel in these hospitals easy and the results as good as those obtained in civil life.

Overseas the situation was slightly different, even in the communications zone. X-Ray equipment had to be portable in nearly all cases, and it was not designed for the elaborate procedures that most gastroenterologists believe constitutes an adequate study of the gastro-intestinal tract. These procedures could be carried out accurately with these machines, but it was not easy, and it required special care and interest to obtain the desired results.

The overseas hospital diet was good, but did not have the flexibility of hospital diets in the United States, and the medical officer was not infrequently puzzled over the problem of constructing a bland, low residue diet or a modification of a sippy regimen. One had to abandon most of his ideas about the elements best suited for a bland low residue diet, and find some way to use the materials at hand. Powdered milk unflavored was not tolerated well as a drink, but if a small amount of chocolate was added and the concoction labelled "milk shake" it was fairly well accepted. Powdered eggs were scrambled in the top of a double boiler, but the results were not too good. One depended to a large extent on cooked cereals, custards and puddings. Meat and potatoes were usually added more quickly to the diet than in civil life because of the sharp limitation in variety of bland foods. Fortunately we were able to supplement these diets adequately with poly-vitamin capsules which were provided by the Quartermaster department for the purpose.

The functional disorders were far less common among combat troops than they were in the troops training in the United States. This was probably because the individuals with the most severe symptoms were weeded out before the troops came overseas. The cases observed by the author in an organization which had seen hard fighting were much more severe than any previously encountered by him. These symptoms were largely pain, nausea and vomiting, and because of them the men had been sent into the hospital as ulcer suspects. There was an unusual persistence of symptoms, the vomiting having almost a cyclic quality in many patients. This group was interesting also because of the fact that in spite of the severity of their symptoms, and the duration (a matter of several months) recovery was complete once the right combination of diet and psychotherapy was found. This was found with trial and error, and individual methods had to be used for each case. It was a source of satisfaction to all concerned to be able to return these men to their

units. The experience gained will aid us in preventing life-long digestive invalidism in many subsequent postcombat cases.

THE DIARRHEAS

The diarrheas constituted an ever present problem in the army. This has been true as long as there have been armies and will probably continue. The common diarrheas usually have their origin in the mess. Overseas it is a problem at times to get the dishwashing water sufficiently hot for adequate sterilization. Only by constant care on the part of the mess officer and inspectors can the kitchens, food handlers, and mess halls be kept clean, and the food supplies properly stored.

In the Sicilian campaign there was much less dysentery than had been expected. The surgeon of one of the Divisions engaged in that campaign was of the opinion that this was due to three reasons: First, adequate water supplies were provided; second, there was good water discipline among the troops; and third, unit surgeons were alert and had insisted on the men reporting the first sign of a diarrhea (4). When a soldier reported on sick call with early symptoms he was promptly given sulfaguanidine, two grams the first day and one gram on the next two days. This controlled the large majority of diarrheas. In this way many soldiers were saved many days off duty.

Amebic dysentery was not a problem in the European theater of operations. The cases that were seen have usually been carriers who had acquired their infestation before leaving the United States.

The most spectacular and crippling type of diarrhea was that caused by the staphylococcus toxin which is heat stable and may be found particularly in ham which has not been properly cared for by the kitchen personnel. This toxin is the cause of the so-called "acute food poisoning" and it lives up to its name. Any group of people eating food containing this substance will become acutely ill in a few hours and be totally disabled for from twenty-four to forty-eight hours. When such an illness knocks out a large number of soldiers it can easily affect the outcome of a battle.

The treatment of "acute food poisoning" was symptomatic but the morbidity was decreased by the use of copious parenteral fluids. Atropine, hypodermically also was of value. In the first few hours it was impossible for these patients to retain anything by mouth, therefore any attempt to administer paregoric, belladonna, or other palliative remedies was futile. One striking symptom often seen was the excruciating muscular cramps in the legs. These were helped by restoration of electrolytes, particularly calcium. This type of intoxication is rare where food is handled carefully.

The nutritional problems encountered in the group known as "Recovered Allied Military Personnel", (contracted to "Ramps") who were American

soldiers previously captured by the Germans and recaptured by Allied troops, were of considerable interest. When first "recovered", their enthusiastic liberators would attempt to feed them large quantities of anything edible or potable from chocolate bars to that liquid dynamite of Normandy called "Calvados". This gave rise to many sudden episodes of nausea, vomiting and diarrhea. Their standard diet had been a bowl of watery soup and a lump of ersatz bread a day. They had augmented this with grass, raw potatoes and an occasional surreptitious handout from nearby enemy civilians.

By the time these individuals had reached United States General Hospitals, the acute phase of their active food intolerance was usually over and they were ready to eat. In fact, when it was practicable they would eat something constantly except when asleep. Their appearance has been described both in "Time" and more recently by Dr. Manfred Kraemer (5). The evidences of Vitamin B deficiency and protein deprivation were marked, but the striking part of the whole clinical picture was the lack of evidence of Vitamin C deficiency. There were no bleeding gums, no petechia or haemorrhagic tendencies of any sort. This may well have been due to the almost universal augmentation of the ration by grass, raw potatoes and raw turnips.

The distressing digestive symptoms of diarrhea and nausea and vomiting were soon controlled by adequate food intake, and the only problems remaining were the care of decubiti, the correction of the nutritional edema, and of the, in many cases, profound psychological changes.

The International Red Cross was instrumental, through its representatives in the camps, in preventing worse treatment than was given our soldiers, but even they were unable to obtain the Red Cross packages for soldiers in the work camps. Soldiers in hospitals were able to get one package, at the most, every two weeks, but usually one package a month. It was notable, however, that those "Ramps" who had been wounded or who had been hospitalized for other reasons in German Hospitals were in far better nutritional condition when "recovered," than those who had remained in the work camps. The ration issued by the Germans was the same in both cases, therefore the difference must necessarily have been due to the Red Cross packages.

GASTROSCOPY

As has been mentioned elsewhere (6) gastroscopy was a useful augmentation to the armamentarium of the gastroenterologist at war, but would have been more so had there been more gastroscopes and more gastroscopists. The specialty of gastroenterology has no place in the active combat zone, and gastroenterologists are not useful as such, further forward than the zone of communications, and their greatest usefulness is in the General Hospitals in the Zone of the Interior where definitive treatment was given.

DEFECT IN ORGANIZATION OF MEDICAL DEPARTMENT

The organization of the Medical Department left no chance for promotion to a grade higher than Major if one wished to remain a clinical specialist. In grades higher than Major, Medical Officers became administrators, as chiefs of services, executive or commanding officers. The various Theater and Regional Consultants in General Surgery, Orthopedic Surgery, Dentistry, Radiology, Anaesthesiology, Oto-Laryngology and Internal Medicine were able to advance, some even to the rank of Brigadier-General, and all, to that of Colonel, and remain in their specialties. Better service could have been given the sick and wounded soldiers had there been Theater and Regional Consultants in Cardiology, Haematology and Gastroenterology, who were able to devote full time to the work and not devote themselves to directing the treatment of pharyngitis and trench foot, as fell the lot of many Chiefs of Medicine in General Hospitals.

REFERENCES

1. CHAMBERLIN, DONALD T.: South, M. J., 38: 523, 1943.
2. CHAMBERLIN, DONALD T.: Am. J. Dig. Dis., 9: 350, 1942.
3. CHAMBERLIN, DONALD T.: J. Med. Assoc. Ga., 10: 40, 1943.
4. COL. W. M. VAN VALEN, MC., U. S. Army: Personal communication.
5. KRAEMER, MANFRED.: Read before the American Gastroenterological Association, Atlantic City, May 24, 1946.
6. CHAMBERLIN, D. T.: Read before the American Gastroenterological Association, Atlantic City, May 24, 1946.

THE DIFFERENTIAL DIAGNOSIS OF 207 HOSPITALIZED CASES OF PEPTIC ULCER

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INTRODUCTION

The present study was made at the Station Hospital, Fort Sill, Oklahoma. In the 16 month period from October, 1942, to March, 1944, there were 1306 enlisted men admitted to the gastro-intestinal section. It soon became apparent that peptic ulcer was the leading gastro-intestinal cause for prolonged hospitalization. It was also found to be a ranking cause for release from the military service on a surgeon's certificate of disability discharge. During this period, 207 soldiers were proven to have peptic ulcer and 200 of them were discharged to civil life. Thus it is apparent that this disease is of importance, medically, financially and from the standpoint of conservation of manpower.

MATERIAL

Of the 207 enlisted men in this series, 200 were shown to have duodenal ulcer and 7 had gastric ulcer. This is a ratio of approximately 28:1. Since there were so few gastric ulcers, no statistical or medical conclusions should be drawn from them. The remainder of this report will be concerned with the 200 consecutive cases of duodenal ulcer.

Rowntree (1) writes of "the very striking racial differences between negroes and whites, culminating in peptic ulcer where there is a ten-fold preponderance in the white males." There were 151 whites and 49 negroes or a ratio of 3:1 in this group. The ratio for the population of the entire post was 8:1 so there were actually nearly three times as many duodenal ulcers in the negro soldiers. In addition, the negro population was more static which would actually exaggerate this ratio further. Thus, any racial difference is extremely doubtful. The soldiers' ages ranged from 18 to 45. The onset of symptoms showed a noticeable "shift to the left." Eleven men dated their onset of present illness from "as far back as (they) could remember," to the ages of seven to ten. Forty five denied all "stomach trouble" prior to the age of 30. The latest onset was at the age of 36. The remainder fell in the second and third decades. The cases were divided into acute (symptoms for less than 1 year) and chronic (symptoms longer than 1 year). There were 27 acute cases averaging 6.5 months. There were 173 chronic cases averaging 5.5 years.

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SYMPTOMATOLOGY

Pain in the mid-epigastrium was present in all but 6 of the cases. Its rhythmicity, chronicity and periodicity are well known characteristics. In one-third of the men this pain did not radiate. In two-thirds there was radiation into the lower portion of the sternum, left chest or back. In one instance there was radiation into the left testicle. In this case pain was relieved by alkali or cream. Genito-urinary studies were normal. Jones (2) has noted radiation of pain from a duodenal ulcer into the scar from an earlier rib resection for empyema.

Careful questioning has brought out the finding of pain more severe late at night in 91%, described as burning in 76%, boring in 72%, accompanied by pain in the mid-back in 49% usually described as an ache. This painful triad has been pathognomonic of duodenal ulcer. Not mentioned in several of the current texts but occurring in 95% of this series was intolerance to greasy foods. No other type of food equalled these as a cause of gastric distress which merely increases the difficulty of evaluating the case history. Considerable vomiting, frequently severe, occurred in 67%.

PHYSICAL FINDINGS

Soreness in the mid-epigastrium was present in 187 of the patients. Weight loss was occasionally extreme, particularly during the hot summer weather. It averaged 13 lbs. for the entire group but there were nearly 50 cases with no change in weight. The "typical ulcer facies" which is subject to a large amount of personal interpretation is here interpreted as being a combination of "lean hungrieness" with unsmiling or perhaps depressed facies and was considered to be definitely present in only 28%. It is frequently stated that the blood pressure is low. Accordingly, pressures were taken on 22 patients with duodenal ulcer and 22 patients with miscellaneous gastro-intestinal disease, all on the same day. Those with ulcer averaged 104 mm of mercury, systolic pressure over 65 mm of mercury diastolic pressure. Those without ulcer averaged 108 mm of mercury systolic, over 68 mm of mercury, diastolic pressure. Rises in temperature above normal were not observed in any cases except those with penetration or severe hemorrhage.

LABORATORY FINDINGS

Here the x-ray is of prime importance since a positive report must accompany each case so diagnosed in all military hospitals. A crater or a tender and deformed duodenal cap determined by fluoroscopy and confirmed by roentgenograms is necessary for a diagnosis. Repeat examinations are often necessary and all doubtful cases have been excluded. A definite niche or

crater was seen in 60 cases. In four it was believed to be penetrating. In only four instances was pyloric obstruction clinically significant, but responded well to treatment.

The white blood counts taken upon admission to the hospital varied from 3,400 to 22,200 with an average of 7,900 per cubic mm. The differential counts were normal in all but 5 instances. There was a polymorphonuclear leucocytosis in all four cases of penetration, which appears to be of considerable clinical importance.

The red cell count and hemoglobin values were within expected normal values except for 10 cases below normal to be discussed.

The sedimentation rate varied from 1 mm per hour to 23 mm per hour. The average was 6.5 mm. Increases above normal were observed only in patients with severe complications.

Fasting gastric analysis followed by the Ewald meal was performed at least once early in the hospitalization before treatment was begun. All cases showing achlorhydria were re-examined sometimes several times and no true achlorhydria was found. However, absence of free fasting acid was noted in 26 cases. Absence of free acid after either the Ewald or alcohol meal or both was noted in 12 cases. There was no case of histamine achlorhydria. The average free fasting acid for all cases was 22.6 units rising to 35 units after test meal. The total fasting acid was 45 units rising to 61.3 units after a test meal. These averages agree closely with Bockus' (3) in 194 cases of duodenal ulcer. Occult blood was present in the fasting contents of 31 cases.

TREATMENT

In the Army, diagnosis receives a high priority because of the necessity of early disposition. Regular ulcer management was withheld in doubtful cases until a gastro-intestinal series was completed. It had been noted that bed, rest and a milk and cream diet with antispasmodics and antacids would in some instances give such immediate relief that a following gastro-intestinal x-ray study five or six days later was occasionally negative. This would be unimportant if all soldiers were available for follow-up. However, soldiers coming from organizations departing for foreign service will be subjected to many factors considered favorable for recurrence of peptic ulcer and overseas facilities should not be taxed by the added burden of this sort. It was decided that more certain diagnosis could be afforded by having the x-ray made during the time of acuteness of symptoms. So well has this procedure worked that in this hospital there were only 2 cases with normal gastro-intestinal x-rays which were believed to have a duodenal ulcer clinically. Likewise, there were several soldiers in whom the diagnosis was considered doubtful because of repeated negative x-ray studies at civilian and other Army hospitals who had a positive x-ray diagnosis of duodenal ulcer made here.

Once the diagnosis was satisfactorily established the patients were put on half milk, half cream feedings of 90 cc which were given every hour until the patient obtained relief. They were then placed on a 21 day standard ulcer progressive diet. Early in the study, nearly every patient received tincture of Belladonna to tolerance and phenobarbital (0.03 gram) two or three times a day. When this antispasmodic and sedative regimen was discontinued in approximately alternate patients of the last 100 admissions, no actual therapeutic benefit could be noted in those who still received it. The antacid powders did not appear to be superior to milk and cream in the reduction of pain but when milk was not obtainable, a measure of relief was nearly always obtained. In a complaint as subjective as epigastric pain and burning, no definite therapeutic conclusions seem possible, however it was the majority impression of subjects that amphoteric liquid was superior to the Sippy powders in this respect. Magnesium tri-silicate was not available for use.

Rigid diets in duodenal ulcer have their sceptics and their adherents. In spite of certain exceptions, it became apparent as this study progressed that these patients did not tolerate the ordinary mess hall diet. Almost any combination of foods prepared according to the instructions given for so-called chronic ulcer, bland, or soft diets had about an equal number of enthusiastic supporters among the patients. However, when they were put back on the mess hall diet, recurrence of epigastric pain and distress was the rule. This was particularly severe when the soldier was fed in the field on the Army canned rations. Trials at duty, following hospitalization and subsequent relief of symptoms, were frequent. In nearly every instance re-hospitalization was necessary in a few weeks or at best, months, unless the soldier was able to eat at home or choose his food at a canteen when available. In one instance a soldier who had requested his return to duty after relief of symptoms, was placed on separate rations and did well until following a week in the field, he developed severe abdominal pain and was re-admitted with a perforation of his ulcer.

COMPLICATIONS

There were 10 admissions for perforation during this period confirmed by operation and with no mortality. Contrary to figures released by the Royal Navy (4) these men did not show an excellent prognosis. They continued to have symptoms when returned to duty and it was necessary to discharge them all from the service while at this station.

There were 10 admissions for duodenal bleeding. It was moderate (red count above 3,000,000) in three, to severe (red count below 3,000,000) in seven. All were placed on a modified Meulengracht diet with hourly feedings continuous for the first 48 hours. There was no further bleeding demonstrable with the exception of one case who continued to bleed for approximately

72 hours requiring two transfusions of whole blood. Their recovery otherwise was uneventful. The red cell count reached normal levels in approximately 5 weeks but there was a lag in the hemoglobin percentage, probably because large doses of iron were withheld early in treatment to prevent possible gastric irritation. An additional 12 cases gave a clear cut history of hematemesis or melena while in civil life. This is an incidence of hemorrhage from duodenal ulcer of 11 percent in the longitudinal study of this disease.

DISCUSSION

In a disease of unknown or controversial etiology, compilation of published clinical material may offer the greatest hope for eventual solution. The observations by physicians of factors which in themselves may seem negligible might furnish an important clue. Certainly there is a great deal of work being done in the subject. Jones (5) in his past two reviews summarizes 104 articles pertinent to peptic ulcer. The Journal of the American Medical Association devotes two issues (6), to a symposium on it. Palmer (7) summarizes from 76 articles.

The history of total abstinence from tobacco in 16% and total abstinence from intoxicating beverages in 35% casts further doubt on the significance of these two drugs in the etiology of this disease, and on its recurrences. It is considered to be simply a matter of individual idiosyncracy when intolerance is present.

No one can conclusively deny that the acidity of the gastric contents is of some clinical importance in the management of peptic ulcer, in the individual case. However, recent articles continue to demonstrate the complexity of the question (8) (9) (10) (11). It appears that further clarification depends on the work with isotopes in gastric secretion (12). In the present series there were 26 cases in which there was no free hydrochloric acid in the fasting specimen. There was no free hydrochloric acid found after an alcohol or Ewald meal in 12 of these 26 cases. Free acid was obtained in every instance after injection of 0.5 cc of histamine phosphate subcutaneously so there was no true achlorhydria, but the old dictum "no acid, no ulcer" has been shown to be diagnostically unsound. Furthermore, there was actually no correlation between the severity of symptoms and gastric acidity. Low values were found in patients with acute symptoms and high values in patients considered convalescent. An exception to this occurred in patients post-operative from perforation. In this group, the acid values were definitely elevated above the average in all but one instance. See figures 1 and 2. The series is too small perhaps to be of significance. These findings confirm Brown and Dolkert's (13) opinion that gastric analysis is of no diagnostic significance.

More impressive than any changes in acidity is the intolerance to "greasy

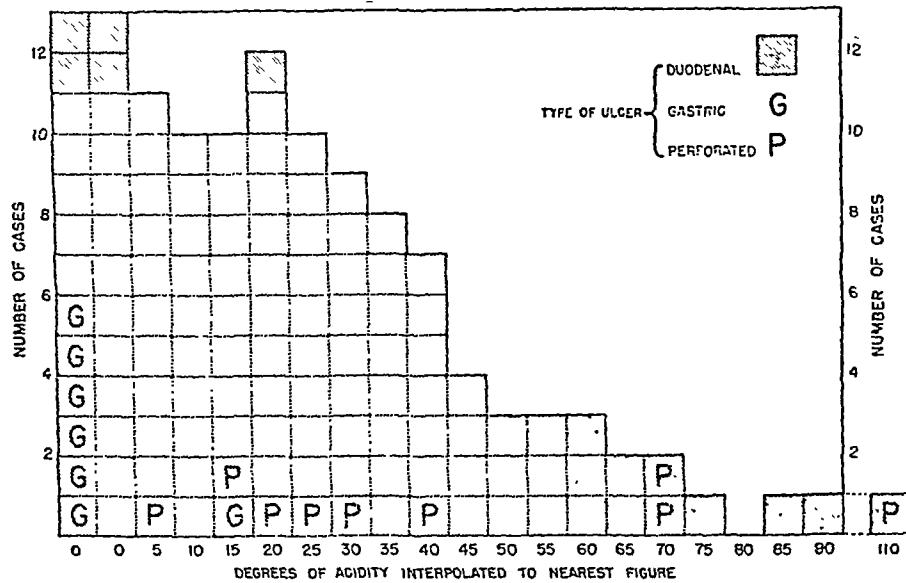


FIG. 1. FASTING FREE HCL DETERMINATIONS

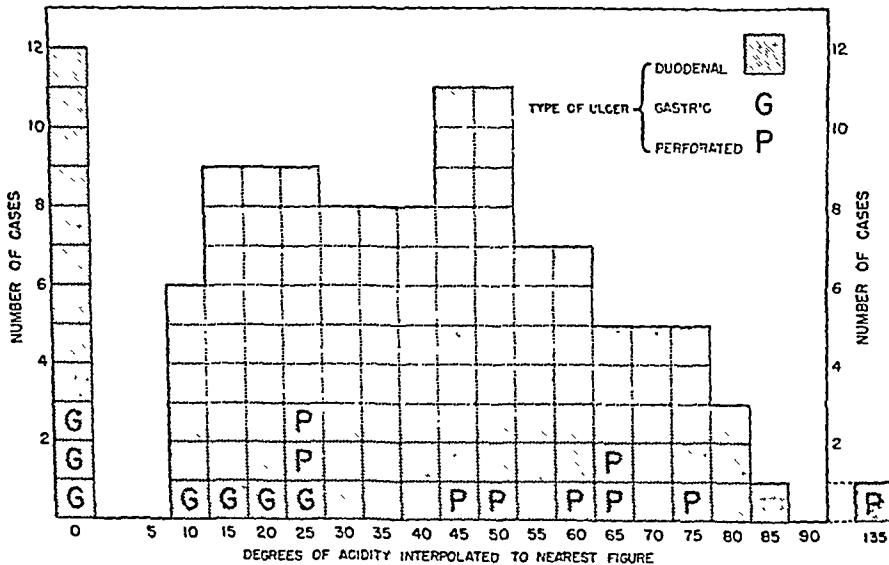


FIG. 2. TEST MEAL FREE HCL DETERMINATIONS

foods." No chemical studies have been possible, but it can't be a failure in fat metabolism because of the comfort afforded by cream. By-products in fat cooking should be intensively studied in an effort to throw new light on this

perplexing problem (14). Recent work on the clinical evaluation of vitamin U (15) may be a further step in this direction.

✓ PSYCHO-SOMATIC ASPECTS

Recent editorials (16, 17) and a review (18) combined with Wolff's work (19, 20) have served to focus sharp attention on the challenge of emotional impacts on the etiology of peptic ulcer. Writers on psychosomatic medicine (21, 22, 23, 24) have added this disease to their growing list of conditions "proven" to be of psychogenic origin. A further impetus to this trend has been the great crucible of Army life out of which has poured much iron but some slag.

Gastro-enterologists in the Army have for the most part been willingly persuaded into the role of understudy to the psychiatric service. This association has proved extremely fruitful for all concerned (26, 27). However, the frequently brilliant accomplishments of the psychiatrists must not blind us to the fact that, to use an extreme example, cancer is still being "cured" by cultists. Intellectual honesty forces us to admit that some of our most grateful patients have been our most mismanaged cases from a medical standpoint.

A summary of Wolff's peptic ulcer case histories showed "prolonged emotional turmoil involving mainly conflict, anxiety, guilt, hostility and resentment." Moschcowitz (25) refers to them as "the haters and the fighters." Most medical officers have seen an appreciable number of soldiers who have self admittedly had all the above emotions, with the possible exception of guilt, preceding and following induction into the Army. The similarity of living, eating and training accompanied by separation from home ties and the uncertainties of a "battle future" would seem to serve as an ideal background for such a study. Likewise, symptoms referable to the gastro-intestinal tract are perhaps the most frequent complaints in psychoneurotic individuals.

Careful analysis of this series has shown a rather marked clinical and emotional difference in the patients with proven peptic ulcer. They have for the most part been quite indistinguishable from soldiers admitted for measles or respiratory disease. They are anxious to return to duty, they were frequently requested to attend sick call, they are cooperative, constructive and what we in the Army refer to as "good soldiers." This is vast contrast to the insecure, emotionally infantile, fearful, blushing, hyperhydrotic, resentful, sick-call repeater whose civilian and Army performance has been sub-standard. A similar opinion has been reached by Walters and his group (28) in a smaller but more carefully studied group of 45 men presenting themselves with gastro-intestinal complaints.

The most surprising result of this entire study was encountered when the admitting diagnosis copied on the patient's record from the dispensary or outpatient visit was compared with the final hospital diagnosis. It was found that

month by month for 16 months the rather frequently changing and large group of doctors were sending in exactly twice as many soldiers diagnosed presumptively as peptic ulcer—observation for, as were eventually so diagnosed. It therefore came about that during the period 200 proven cases of duodenal ulcer were observed side by side with 200 cases in whom x-ray studies were normal or at least were not those of ulcer. More often than not this diagnosis had been given them in civil life by their own physicians, either in spite of normal x-ray studies or without any. Observation of this latter group gradually revealed rather important differences from the ulcer group. A large number of these "inherited a weak stomach from their mother or father." More intensive questioning usually revealed a much greater variety of complaints with usually several systems involved. Consultants called to see them frequently recognized old friends formerly on the cardiac, genito-urinary or orthopedic wards. Management with standard ulcer treatment gave remarkably little subjective improvement. The epigastric distress was more variable and much more frequent after eating; vomiting was considerably more frequent but resulted in less weight loss. It is not the purpose of the author to go any more deeply into this comparison as it was the outcome of, rather than the initial purpose of the study. However, it seems to be the cause for a great deal of the rather loose thinking associated with the ulcer problem. Surely it seems to answer the perplexing statements that rather high percentages of duodenal ulcer will not be picked up by x-ray. It probably accounts in part for the surprising success of some remarkably unsound medications advised from time to time in the literature as well as for failures.

In conclusion with regard to the ulcer cases, it is not to be supposed that they were universally free from neurotic traits. Approximately 10% with a proven crater or deformity were definitely diagnosed as having accompanying psychoneurosis. Their management proved fully as difficult as those cases without ulcer. However, it was generally considered by the Chief of the Medical Service and others, that the peptic ulcer patients as a whole showed no greater or less degree of psychiatric imbalance than the patients with organic heart disease, tuberculosis or diabetes.

SUMMARY

1. 200 consecutive cases of duodenal ulcer and 7 cases of gastric ulcer have been followed under hospital management and reported in this paper.
2. There has been no racial difference between white and negro soldiers culminating in peptic ulcer.
3. Mid-epigastric pain occurring late at night and radiating into the mid-back appears diagnostic of active duodenal ulcer.
4. No correlation has been obtained between the gastric analysis and the

severity of the ulcer or of the complaints. Absent free hydrochloric acid occurs in both the fasting (26 cases) and test meal (12 cases) contents.

5. An increase in the total count and the percentage of polymorphonuclear cells in strong evidence of a penetrating ulcer and does not occur in the absence of complications.

6. A duodenal ulcer has a 10% chance of producing serious bleeding, and a 5% chance of perforating during its course.

7. Alcohol and tobacco are not implicated as etiological factors in this disease.

8. The x-ray proof of this disease should be expected in over 90% of all cases and was present in 100% of this series.

9. A comparison has been afforded by the inclusion of 200 other cases diagnosed as peptic ulcer but not so proven which does not support the emotional concept of the genesis of duodenal ulcer.

REFERENCES

1. ROWNTREE, L. G., COL, MC: The Unfit: How to Exclude Them. American Soc. for Research in Psychosomatic Problems. Proc. of the Military Session, Detroit, 1943, May 9.
2. JONES, CHESTER: Personal communication.
3. BOCKUS, H. L.: Gastro-Enterology. Vol. I, W. C. Saunders & Co., Philadelphia, 1944.
4. Editorial: Amer. Jour. Roent. Rad. Ther., 51: 237, 1944.
5. JONES, C. M.: Arch. Int. Med., 70: 585, 1942; 73: 53, 1944.
6. Panel Discussion on Peptic Ulcer: J. A. M. A., 120: 733, 1942; 120: 811, 1942.
7. PALMER, W. L., HARMON, D. S., AND RICKETTS, W. E.: Arch. Int. Med., 75: 251, 1945.
8. DAVENPORT, H. W.: Am. Jour. Digest. Dis., 9: 416, 1942.
9. SHAY, H., GERSHON, COHEN, J., FELS, S. S., AND SIPLET, H.: Am. Jour. Digest. Dis., 9: 363, 1942.
10. IVY, A. C., AND GROSSMAN, M. I.: Gastroenterology, 4: 438, 1945.
11. BECK, J. E., THOMAS, J. E., AND REHFUSS, M. E.: Am. Jour. Digest. Dis., 9: 371, 1942.
12. ROSS, J. F.: New Eng. J. Med., 228: 454, 1943.
13. BROWN, C. F. G., AND DOLKERT, R. E.: Arch. Int. Med., 60: 680, 1937.
14. SMITH, C. S.: Ohio State Med. J., 39: 425, 1943. See also Heated Fats and Stomach Cancer—Nutrition Reviews 3: 42, 1945.
15. CHENEY, G.: The Military Surgeon, 95: 446, 1944.
16. CROHN, B. D.: Am. Jour. Digest. Dis., 9: 358, 1942.
17. PALMER, W. L.: Gastroenterology, 1: 232, 1943.
18. JONES, C. M.: New Eng. J. Med., 228: 612, 1943.
19. WOLF, S., AND WOLFF, H. J.: J. A. M. A., 120: 670, 1942.
20. MITTELMAN, B., AND WOLFF, H. G.: Psychosomatic Medicine, 4: 5, 1943.
21. DUNBAR, H. F.: Emotions and Bodily Changes. 2nd Ed., Columbia University Press, New York, 1943.
22. WEISS, E., AND ENGLISH, O. S.: Psychosomatic Medicine. W. B. Saunders Co., Philadelphia, 1943. See also Alvarez, W. C.—Gastroenterology, 4: 355, 1945.
23. LIPKIN, M., AND SHARP, L. I.: Arch. Int. Med., 20: 760, 1944.
24. VORHAUS, M. G., AND ORGEL, S. Z.: J. A. M. A., 126: 225, 1944.
25. MOSCHCOWITZ, ELI: Am. J. Med. Sci., 206: 576, 1943.
26. RUSH, A.: J. A. M. A., 123: 471, 1943.
27. AITKEN, D. G.: J. of R. A. M. C., 81: 223, 1943.
28. MONTGOMERY, H., SCHINDLER, R., UNDERDAHL, L. O., BUTT, H. R., AND WALTERS, W.: J. A. M. A., 125: 890, 1944.

CORRELATED GASTROSCOPIC AND PSYCHIATRIC STUDIES OF SOLDIERS WITH CHRONIC NON-ULCERATIVE DYSPEPSIA*

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INTRODUCTION

Soldiers who complain of chronic epigastric distress, heartburn, vomiting and upper abdominal pain without demonstrable organic etiology make up a large group which constituted a major medical problem in this war. (Halsted and Weinberg (1) demonstrated that 78 per cent of 100 such patients studied in a Base Hospital had psychogenic factors which could be considered to be the cause of the symptoms.) Because gastroscopic observations were not made the presence of gastritis could not be ruled out.

(Montgomery et al. (2) reported the first series of cases studied by both gastroscopic and psychiatric methods. This study was conducted in a Navy Base Hospital. (While these authors demonstrated that 80 per cent of the patients had some degree of psychoneurosis and 50 per cent some form of gastritis no correlation was drawn between the emotional state and its possible effect on the gastroscopic picture, the impression being gained that patients presenting both conditions had two diseases.) Schwartz and Perlmutter (3) have made an extensive gastroscopic survey among 122 soldiers overseas in a General Hospital, all complaining of chronic epigastric distress. In this group 9% had organic disease. Of the others 70% had a demonstrable psychoneurosis and 46% of the total showed gastric changes. Of those with psychoneurosis 60% showed gastroscopic changes.)

In none of these studies has a systematic attempt been made to evaluate the role of emotional factors as a possible cause of the mucosal changes which are seen gastroscopically in a certain percentage of patients. It was the purpose of the present study to make such an attempt. In addition an attempt has been made to throw light on the etiology of symptoms by analysis of the patients' histories in relation to the gastroscopic findings.

METHOD OF STUDY

110 consecutive and unselected patients complaining of chronic dyspepsia were carefully studied by clinical, roentgenographic, psychiatric and gastro-

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scopic observation. These patients were combat soldiers who were admitted to a forward medical installation in the Fifth Army Area in Italy which was designated as a Gastro-intestinal Center.⁶ The purpose of this center was to provide facilities where patients with gastro-intestinal complaints could be diagnosed rapidly, with evaluation of fitness for duty in an area close to the front. The practical military value of this procedure was based on the fact that the majority of such patients represented psychosomatic syndromes, prolonged hospitalization for which produced intensification of symptoms and consequent loss of manpower. Seventy per cent of the 776 patients studied at this center were admitted direct from Divisional Clearing Stations a few hours after leaving the front, the remainder being referred from Evacuation Hospitals for study.

The patients included in this investigation were studied during a period of seven weeks immediately preceding the last offensive on the Italian front when the break-out into the Po Valley occurred. Tension among the troops was quite high owing to anticipation of a difficult campaign after enduring a winter of cold and wet conditions of static warfare in the North Appennines. Owing to the static front existing at the time it was possible to study the patients as adequately as could be done at a Base Hospital in the rear. The only criterion for selection of patients was a presenting complaint of chronic dyspepsia of at least three months duration. Personnel consisted of two internists (J. A. H. and I. R. S.) one of whom (I. R. S.) was an experienced gastroscopist, a psychiatrist (S. R. R.), a roentgenologist (S. M. W.), and a clinical psychologist (H. W.). Upon admission the patient's medical history was obtained, a physical examination made, stool, urine and hemoglobin examinations ordered. The following morning gastro intestinal roentgenographic study was carried out. The clinical psychologist then interviewed the patient in order to obtain a life history. Following this the psychiatrist examined the patient in order to form his opinion as to whether the patient had a clinical neurosis, or merely a background of neurotic traits; whether there was free anxiety resulting from combat or whether the patient was normal psychiatrically. After this the patient was gastroscoped. This detailed investigation occupied from three to five days for each patient. Bi-weekly conferences were held at which each case was thoroughly discussed in order to arrive at agreement as to the psychiatric status, to decide upon disposition and to correlate all clinical findings. The evaluation of psychogenic factors was easy and without disagreement in the large majority of cases. In some, however, the significance of neurotic traits could only be evaluated after conference, subsequent interviews and observation of the patient's behavior on the ward.

⁶ We are indebted to Brigadier General Joseph I. M...^{...}, M.C., U.S.A., Fifth Army, for his cooperative interest in psychosomatic problems by making the ... Hospital available, and to Colonel John A. Evans, M.C., A.U.S., Commanding Officer of this hospital.

The gastroscopies were performed in a darkened pyramidal tent set up on a wooden frame. This also served as the office. The omniangle flexible gastro-scope (Cameron modification of Schindler) was used. The stomach was emptied prior to introduction of the gastroscope, the fluid obtained being titrated for free hydrochloric and total acids. Routine gastric analysis, using a test meal, was not carried out as it was considered to be without important value in the study of chronic dyspepsia in the soldier age group.

From the entire group, ten men were selected whose degree of anxiety precluded sending them back to full duty. They were sent to the Fifth Army Convalescent Hospital for two to three weeks of rest and relaxation after having been informed that they were to be reclassified to a noncombatant status. At the end of that time they were returned to the Gastro-Intestinal Center, interviewed by the psychiatrist to determine any changes in their emotional status, and regastrospected to see if the lessening of anxiety had affected the previous gastroscopic picture.

RESULTS OF STUDY

✓ *1. Clinical features.* As in other similar studies of soldiers with non-ulcer dyspepsia those in this series presented a fairly uniform clinical picture. The majority had had symptoms for several years. Symptoms started before entry to the Army in 75 or 68 per cent, after entry to the Army but before coming overseas in 11 or 10 per cent and after arrival overseas in 24 or 22 per cent. Characteristically there was little or no remission when the patient felt entirely well regardless of what he ate. Often the symptoms had never been severe until entry into the Army and at each episode involving entry into a less stable or more dangerous there had been an exacerbation. Frequently patients were hospitalized at these times. When this was done little improvement was admitted and the patient often said, "They didn't tell me what was wrong" or "They said it was a nervous stomach but I am sure it was those C rations."

✓ Usually the patients complained of epigastric distress of a diffuse nature, a burning feeling, or heartburn while eating or directly afterward. This rarely came on after an interval of time following eating. They usually had a good appetite but felt full after a few mouthfuls. Soda occasionally gave relief but food rarely did.) "Vomiting" was common, but on close questioning it usually proved to be regurgitation of a few mouthfuls. Occasionally the patients vomited after breakfast regularly, sometimes for a long period of time. Altered bowel habits were very uncommon. Nearly always the patients looked well, were not malnourished nor dehydrated. Not infrequently patients related their gastric distress to exertion rather than to eating. Characteristically there was no symptomatic improvement as a result of the employment of dietary or medicinal therapy.

Very commonly these patients had other symptoms such as dizziness or light-headedness, insomnia, inability to relax, pains in the chest or palpitation, headache, etc. As in many psychoneuroses the patients complained of feeling tired, particularly in the morning.

✓ A family pattern of indigestion was elicited in 56 per cent of the patients in this series. The patients frequently had had lifelong dislike of certain foods, being very fussy about what they were able to eat. Although being convinced in their mind that diet was the cause of their symptoms these patients rarely felt any better when given a bland diet in the hospital. (What they unconsciously or consciously wanted was relief from unpleasant duty and usually if a decision was made to reclassify them to non-combat duties they complained very much less.) However, relief from duty does not result in cure. The mechanism is much deeper and more complicated than mere reaction to an unpleasant situation in the majority of patients. It is believed that malingering is very rare as a cause of dyspepsia, although there may be conscious exaggeration of symptoms.

The personality pattern was rather uniform and was strikingly different from that of peptic ulcer patients. They were outwardly submissive and unaggressive but underneath one could sense a pronounced degree of hostility and resentment. It was usually difficult to achieve rapport with these patients. They showed abnormal concern over the stomach and magnified symptoms with obvious desire to impress the medical officer with the gravity of their distress. They rarely felt well, were usually tired and had other complaints.

(Physical examination rarely revealed any abnormalities except for diffuse upper abdominal tenderness, and sometimes signs of vasomotor instability such as moist palms or tachycardia.)

Laboratory examinations in the group of patients did not show any significant abnormalities in hemoglobin, urine or stool examination. Titration of specimens of fasting gastric juice obtained on emptying the stomach prior to gastroscopy revealed varying degrees of acidity. These results had no relationship to the symptoms, to psychiatric status, nor to gastroscopic findings and will not enter further into the discussion.

✓ 2. *Gastroscopic findings.* Mucosal changes deviating from the normal were encountered in 41% of the patients. Only two cases classified as hypertrophic gastritis were seen. No cases of gastric atrophy were observed. The remainder fell into the category of superficial gastritis as described by Schindler (4). The changes observed were varying degrees of redness, edema and adherent mucus. Occasionally small submucosal hemorrhages were seen.) The changes were graded on the basis of mild, moderately severe and severe depending on the degree and extent of involvement. Schindler notes that exudation is the most important characteristic of superficial gastritis. This is not the exudation

caused by regurgitation from the duodenum, swallowing of saliva or hypersecretion of an irritable stomach but adherent grayish or white exudate. In several patients who were unusually tense a profuse hypersecretion occurred. Whether this was caused by the underlying anxiety of the patient or merely a reaction to the gastroscopic procedure could only be answered by the examination of many normal subjects.

Notation was made of any spasm that was encountered during and after introduction of the instrument. Whenever spasm was noted the patient was questioned as to whether he felt distress and whether this was similar to his usual distress.

A total of 126 gastroscopies were performed on 113 patients, three of whom had duodenal ulcers. Two patients who had been completely studied were not included because of unsatisfactory visualization of the gastric mucosa. Another patient had a hysterical reaction while being prepared for gastroscopy. Because of the possibility that this reaction might have been due to cocaine sensitivity, attempt at further examination was abandoned.

Of the 110 patients with non-ulcer dyspepsia who were studied, the following findings were obtained. 59 per cent had a normal gastric mucosa. 26 per cent demonstrated slight or mild changes in the gastric mucosa consisting merely of redness and edema. 15 per cent showed more marked and extensive changes with edema, redness and adherent exudate. There were no cases of ulcerative or severe hypertrophic gastritis. In seven cases spasm of the antrum or mid-body was encountered during the gastroscopic examination. Gastroscopic abnormalities accompanied this spasm in only two cases. In the other five instances the gastric mucosa was normal. Two of these five patients volunteered the information that the pain experienced during the gastroscopy was exactly like the pain for which they were hospitalized. The other patients were unaware of any painful sensations during the procedure.

It is necessary to explain why this group of 110 soldiers with chronic non-ulcer dyspepsia showed 39% superficial gastritis, 2% hypertrophic gastritis and no case of atrophic gastritis whereas other series (2) (5) show much higher percentages of hypertrophic and atrophic gastritis. Firstly, we were dealing with infantrymen in combat. The other reports deal with soldiers in the United States. Both Benedict (6) and Annis (5) comment on the fact that hypertrophic gastritis is often accompanied by an ulcer-like symptomatology. Such patients would be more likely to be excluded from overseas service. Patients with atrophic gastritis often have systemic symptoms in addition to dyspepsia and would be unlikely to get as far as the front lines. As Jones (7) has pointed out this is probably a manifestation of nutritional deficiency and more properly should be called gastric atrophy rather than atrophic gastritis. Secondly, hypertrophic gastritis and gastric atrophy are usually seen in older

patients than combat infantrymen generally are. Thirdly, there may be differences in interpretation of findings among different gastroscopists.

The number of patients in our group showing gastroscopic abnormalities, 41%, approximates the percentage reported by Montgomery, et al (2) who found 50%, by Annis (5) who found 39.5%, and by Schwartz and Perlmutter (3) who noted 46%. It is interesting that only 3 cases of duodenal ulcer were found in this series. (This makes 2.3% of 113 cases.⁷ In each case the ulcer was located in the duodenum and the diagnosis was made clinically and confirmed by roentgenographic study.) Each ulcer patient was also gastroscoped to determine the presence of gastritis. Two showed mild mucosal changes similar to those found in the non-ulcer cases. The third was normal.

Of 10 patients showing signs of gastritis who were reclassified to non-combat duties and, after a two weeks rest at the Convalescent Hospital, were regastroscoped, little change was noted in the gastroscopic picture. One showed slight changes at the first examination and a normal mucosa at the second. Four showed moderate changes at the first examination and only slight changes at the second. Four had moderate changes at each examination, and one had a slight change at both examinations. Important to note however, is the fact that in spite of there being little change in the gastroscopic picture the symptoms became markedly lessened or disappeared in 8 out of the 10 patients. Of the other two patients one had a complicated lifelong neurosis and hysterical vomiting. He showed moderate changes at the first examination with slight changes at the second yet was not improved symptomatically. The last patient had no psychiatric abnormalities, was a 40 year old infantryman with gastric symptoms of three years duration. His symptoms were mild and did not change although the gastroscopic picture was entirely normal at the second examination, having shown slight changes at the first. Although there are too few patients studied in this way to draw conclusions, these observations indicate that symptomatology was relieved by reducing nervous tension, but that this was not accompanied by any significant change in the state of the gastric mucosa. It is additional evidence to the contention of others (9) (10) that the severity of symptoms of symptoms has no bearing on the presence or absence of gastroscopic abnormalities.⁸

3. *Psychiatric observations.* Detailed discussion of the psychiatric aspects of this group of patients and of psychodynamics will not be presented here as this is to be the subject of another report by Rosen et al (12). Certain statistical data bearing on the incidence of neurotic traits will be presented for what

⁷ The infrequency of new peptic ulcer seen among combat soldiers in Italy has been noted by Halsted and Weinberg (8).

⁸ Schwartz (11), in gastroscoping 20 soldier patients 10 to 14 days following an outbreak of acute food poisoning, found no correlation between the appearance of the gastric mucosa and the gastric symptomatology.

they are worth but conclusions will not be drawn from this data inasmuch as accurate knowledge is not yet available for normal individuals. A family history of chronic dyspepsia was present in 56 per cent, the father being the most commonly affected member.) This high incidence of familial predisposition has been noted in all studies of dyspepsia and may represent identification of the dependent neurotic individual with a parent.) Anxiety phobias such as fear of the dark or of high places, faintness at sight of blood, apprehensiveness in the presence of an accident or a fight existed in 50 per cent.) Enuresis to at least the age of 10 occurred in 26 per cent.) A broken home, such as separated or incompatible parents or other serious family discord was present during the childhood of 38 per cent of the group. (Of 56 patients who had married 10 or 18 per cent were divorced.) Nailbiting occurred in 20 per cent. Alcoholism of significant degree existed in the past in 18 per cent. This was a manifestation of neurosis rather than of constitutional psychopathy. Since entry into the Army most of these patients claimed they no longer drank to excess.

✓ Among the 110 patients 17 (15.5%) were psychiatrically normal and 93 (84.5%) had positive evidence of a psychoneurosis. In 81 of the 93 with a diagnosis of psychoneurosis a neurotic mechanism and neurotic reaction to life could be traced back many years. It was not a mere reaction to the combat situation, a simple escape phenomenon, but a neurosis which would be recognized in civilian life. In the other 12 although there were neurotic traits in the past history, the neurotic behavior of the patient was a temporary phenomenon resulting from the combat situation.

The symptoms of three of the 17 normal patients suggested peptic ulcer and responded moderately well to treatment with a bland diet (one responded completely). In none of the patients were any significant psychiatric features present, their adjustment to life having been adequate. However their digestive symptoms were entirely similar to those with a neurosis (except for the three with an ulcer-like syndrome) and these symptoms were unimproved by treatment. It was thought that they might have deep seated anxiety because the symptomatology was so similar to those with a neurosis. However, if such was the case, the psychiatric methods were inadequate to demonstrate it positively in the available time.

The 93 patients with a definite neurosis had various manifestations but were of three main types from a descriptive point of view. 62 had many neurotic traits in their backgrounds, such as anxiety phobias, enuresis, uneasiness in the presence of authority, etc., reacted neurotically to important situations throughout their lives, and usually had stomach symptoms of many years' duration. 12 patients had neurotic traits in the past but had been able to adjust to life reasonably well both before and after entry to the Army. However, when faced with a situation which was too difficult for them they

developed stomach symptoms and other neurotic behavior. The environmental situation may have been an overbearing superior officer, or stress of combat with resultant hostility and resentment on the part of the patient. The anxiety engendered by the environmental situation was considered to be an adequate explanation for symptoms. 19 patients had objective signs of free anxiety resulting from combat, such as tremor, apathy, depression or insomnia. These patients were aware of being nervous and, in contrast to the others, could connect their nervous feeling with their stomach symptoms.

Certain factors were important in respect to social aspects. Thus the military record was satisfactory in all but 8 patients and they had served success-

TABLE I

PSYCHIATRIC STATUS	TOTAL	NORMAL GASTRIC MUCOSA	GASTROSCOPIC ABNORMALITIES
Normal.....	17 (15.5%)	6 (35%)	11 (65%)
Neurosis.....	93 (84.5%)	59 (63.5%)	34 (36.5%)
Total.....	110 (100%)	65 (59.2%)	45 (40.8%)

TABLE II
Duration of symptoms

DURATION OF SYMPTOMS	NORMAL GASTRIC MUCOSA	GASTROSCOPIC ABNORMALITIES
3-12 mos.....	9	10
1-5 yrs.....	14	16
5-10 yrs.....	15	5
More than 10 yrs.....	27	14
Total.....	65	45

fully in combat for an average of 6 months. 50% of the group were non commissioned officers. The neurotic soldier is often a good soldier if he has proper leadership, good training and proper medical management. Improper medical management, consisting of prolonged medical investigation in hospitals in an attempt to find organic disease, is devastating to morale and fitness for further duty. Thus it was found that 80 per cent of patients with psychogenic dyspepsia could be returned to duty from the Fifth Army Gastro-intestinal Center and only 55% of patients with a similar degree of neurosis could be returned to duty from a General Hospital, the latter having been hospitalized three or four times as long as the former group. Eighty-three per cent of those returned to duty from the Army Gastro-intestinal Center performed satisfactorily in combat for one and one half to four and one half months after discharge (13).

A correlation between the psychiatric status and the gastroscopic findings is indicated in table I. Relationships between gastroscopic findings and duration of symptoms are shown in table II. It will be seen from table I that 65% of the 17 psychiatrically normal patients had an abnormal gastric mucosa. Only 36.5% of the 93 neurotic patients had an abnormal gastric mucosa. The significance of these figures is open to question on two grounds. First the number of patients without neurosis is too small to be of statistical importance. Second, in only three of that group were we convinced that there was actually no psychogenic factor. In the other 14 the symptomatology was similar to the neurotic group (vagueness of digestive complaints, lack of response to treatment, multiplicity of symptoms, etc.), yet one could not find objective evidence of neurosis. Had there been more time available for psychiatric investigation it is probable that a psychogenic factor would have been demonstrated in some of the 14 because this had been found frequently to be the case in follow-up at subsequent hospitalization in other similar cases. No conclusions are drawn from the fact that patients with a normal gastric mucosa tended to have had a longer duration of symptoms than those patients showing gastroscopic abnormalities. Important to note, however, is the fact that patients who showed gastroscopic abnormalities presented no differences in symptomatology from those with a normal gastric mucosa.

DISCUSSION

The mechanism of the epigastric distress in patients with chronic non-ulcer dyspepsia is not clear. That it is not wholly the result of mucosal changes as seen gastroscopically seems undoubted for the following reasons. Firstly, there is no difference in the symptoms of patients who have the changes and those who do not. One cannot predict from the type of symptoms, their duration, nor from the psychiatric status of the individual whether or not deviation from the normal will be found at gastroscopic examination. Secondly, mucosal abnormalities may be found in patients who have no complaints, as Schwartz (11) has demonstrated in his gastroscopic study of 20 patients following an attack of acute gastro-enteritis from food poisoning. Normal individuals who have never had gastric symptoms may have abnormalities of the gastric mucosa as Fitzgibbon and Long (14) demonstrated in 5% of 40 students. Thirdly, in 10 neurotic soldiers with dyspepsia and mucosal abnormalities the symptoms lessened with decrease in anxiety, yet the mucosal changes remained essentially the same.

A plausible explanation for the mechanism of the distress may be found in abnormalities of motility producing spasm of the body of the stomach. Evidence for this has been found in this study by the demonstration of marked mid-body spasm at gastroscopy in 7 patients, two of whom stated that they felt

pain at the time the spasm was observed which was exactly similar to the pain of which they complained constantly. In only two of these 7 patients were any mucosal abnormalities noted. These were not the same patients who associated their usual pain to the observed spasm.

Even though the evidence is against so-called chronic superficial gastritis of itself as being the direct cause of gastric symptoms, nevertheless these inflammatory signs may be associated with hyperirritability making such a stomach more excitable with resultant abnormalities of motility. Wolf and Wolff (15) demonstrated that vigorous contractions of the stomach were found to induce pain and that sensitivity to this pain was increased in the presence of hyperemia and engorgement of the mucous membrane. Clinical observations suggest that the mucosal changes, at least as regards chronic superficial gastritis, are a somatic change accompanying an emotional disturbance and not an independent inflammatory disease. It is logical to assume that the motor changes herewith noted are a parallel phenomenon.

✓ The evidence in favor of mucosal changes being directly related to emotional conflict may be summarized briefly. The studies of Wolf and Wolff (15), so widely quoted recently in gastro-enterological literature, offer the strongest objective evidence that emotional tension may result in marked changes in the gastric mucosa. Their subject with a gastric fistula illustrates the point that a state of emotional tension manifested by fear, hostility, resentment or sustained anxiety, results in marked changes in gastric motility, secretion and vascularity. Reddening and engorgement of the mucous membrane were noted, often reproducing the picture of "gastritis" as seen by gastroscopy. When the emotional tension was relieved the mucosa returned to its normal appearance. Although Wolf and Wolff call these changes those of hypertrophic gastritis in their book, Dailey (16) has criticized this, calling attention to the fact that the changes they describe are actually those of superficial gastritis rather than of the hypertrophic variety. We are in agreement with this criticism but emphasize the fact that the gastroscopic abnormalities seen in our series are similar to the mucosal changes described by Wolf and Wolff.

✓ Beaumont (17) in 1833 found similar congestion of the mucosa of the stomach of Alexis St. Martin during distressing emotional states but did not describe these emotional states in detail.

It would be trite to call attention to the numerous well known studies of the effect of emotions on gastro-intestinal function. Furthermore they are not entirely relevant inasmuch as they have related to other physiological effects such as changes in motility, chemical alterations, and blood flow rather than to the appearance of the mucosa with which this discussion is concerned. Suffice it to say that emotional tension may produce gastro-intestinal discomfort.

Do the observations recorded in this paper warrant a conclusion that the

gastroscopic abnormalities noted are the result of functional circulatory changes caused by psychogenic disturbances, rather than the manifestations of an organic disease? The final answer to this question cannot be given from the evidence at hand although it is suggestive that such is the case since at least 75% of the patients with gastroscopic changes had a neurosis which in itself was causing some degree of disability. From a consideration of the psychodynamics of gastric disturbances an explanation for symptoms on a neuropsychological basis may be reached. (Portis (18) sums this up as follows: "That the digestive tract should be the seat of altered emotional response is best explained anatomically on the basis of its abundant afferent and efferent nerve supply. The ease of transmission of emotional stimuli from the hypothalamic region to the digestive organs is a common observation. Furthermore there is no other vital function which from early life plays such an important role in the emotional household as eating. The relief from physical discomfort that the infant experiences while eating and the satisfaction of hunger become deeply ingrained in the child, being associated with a feeling of well being and security.) To the child feeding and love become inseparable. This oral receptive manifestation in early infancy is the natural emotional state of the child. If it persists in later life it must be suppressed, because it is not harmonious with independent adult life. The repressed oral trends may produce a disturbed function leading to changes in the physiologic equilibrium. The stomach may reveal this evidence of disturbance by becoming red, turgescent and edematous; it may be thrown into various spasms and become hyperirritable, and changes in the secretory apparatus may become manifest."

Howard (9) states, "The clinical courses of patients who have vague upper abdominal symptoms and, as their sole objective finding, chronic gastritis, suggest that these symptoms are more likely to be on a psychogenic basis than to be mere manifestations of gastritis." Schindler's (19) suggestion that the neurotic symptoms in a patient with gastritis may be caused by the gastritis, could hardly be tenable in our group when one finds on psychiatric study that the neurosis in the majority of cases is very deep seated, extending back into childhood. Furthermore it is difficult to conceive that the stomach should show such slight degrees of redness, edema and exudation as was noted in 26% of the 41% of cases with an abnormal mucosa, in patients who had had symptoms for many years, if these changes were signs of an organic disease.

Certain observations in this report may be cited as being against a psychogenic etiology for the gastroscopic abnormalities. Little change occurred in the mucosa of the 10 patients whose anxiety was lessened by removal from combat duty in spite of the fact that symptoms largely disappeared. However, the symptoms were of several years' duration in all but two cases. The neurotic mechanism was much more complicated than mere anxiety from bat-

tle or fear of shells. Removal from combat only relieved a superficial tension. Furthermore, reclassification on the basis of psychoneurosis has been found to be followed often by distinct guilt feelings, a sense of "letting his buddies down," thus further complicating the neurotic mechanism. The experiment was therefore inconclusive because the psychotherapy employed (changing the environment) was superficial.

The finding, by Schindler and Ortmayer (20) and Bendict and Mallory (21) of a correlation between the gastroscopic abnormalities and the histologic structure of the stomach obtained by biopsies and resection has been cited as an argument that the gastroscopic abnormality is a sign of an inflammatory disease. In superficial gastritis microscopic section revealed extensive infiltration of polymorphonuclear leucocytes into the interstitial tissues of the upper portions of the mucosa. In connection with this however, Alexander (22) and others have pointed out that functional disturbances in an organ may in time lead to organic tissue changes. This fact could explain the histological changes reported. It also makes it likely that disappearance of mucosal changes coincident with relief of chronic emotional tension through psychotherapy may be hard to effect. Nevertheless further attempts at making such correlations are needed in order to elucidate the etiology of so-called chronic superficial gastritis.

✓ The effect on the gastric mucosa of alcohol, tobacco, coffee and a deficient diet must be considered in our group of cases. It is known that all four of these factors may cause changes in the stomach. In the case of alcohol 20 patients were heavy drinkers in the past but such had not been the case during at least several weeks preceding admission. Soldiers in the lines have little opportunity to drink. Nearly all soldiers smoke heavily but the patients who had a normal mucosa smoked as much as those who had abnormalities. The effect of caffeine on the gastric mucosa has been studied by Roth, Ivy and Atkinson (23). They produced diffuse areas of epithelial desquamation with multiple bleeding erosions and ulcerations of the gastric mucosa in cats by administering caffeine and histamine. They hypothesized that 10 to 15 cups of coffee daily might contribute to the development of ulcer in man. Soldiers nearly all drink coffee but it is not possible for them to get much more than 3 or 4 cups daily particularly in the field. It would seem unlikely that caffeine was the cause of the abnormalities seen in the mucosa.)

✓ Dietary deficiency may cause abnormalities in the mucus membrane of the gastro-intestinal tract. The diet of soldiers on field rations is not deficient if he eats it all. However, he rarely does eat the entire ration which becomes unpalatable after a few days. But in the period during which this study was undertaken and for the preceding four months the front had been relatively inactive, making it possible for frequent relief from front line duty. When such

relief occurred hot food became available. It is most unlikely that nutritional deficiency would occur. Objective signs of vitamin deficiency were exceedingly rare among American soldiers. Thus it is believed that dietary deficiency can be ruled out as a cause of gastric mucosal abnormalities.

As mentioned above the evidence is strongly suggestive that the symptoms of soldiers with chronic non-ulcer dyspepsia are caused, not by an inflammatory disease, gastritis, but by psychoneurosis. Abnormalities of motility rather than mucosal disturbances is the most likely direct explanation of the symptoms. If such is the case what should be the place of gastroscopy in the management of soldiers with dyspepsia? Is it of any value in the diagnosis, treatment, or decision as to what may be required of the soldier in respect to further duty? Does it do any harm? All studies give roughly the same results, namely around 40% of cases showing gastroscopic abnormalities. However it is highly debatable whether any weight in respect to treatment should be given findings of the nature reported in this series. Army experience overseas shows that patients respond little or not at all to medicinal or dietary therapy regardless of whether the mucosa is normal or abnormal. The therapeutic approach adopted by the authors was almost entirely a psychiatric one. Decision regarding disposition of the patients was made on the basis of severity of the neurosis, little or no attention being paid to presence or absence of symptoms, as it was found that symptoms persisted or even grew worse the longer patients were hospitalized. Actually the symptoms of a few patients improved after they returned to combat duty, as was discovered in a follow-up study.

In neurotic patients gastroscopy may be undesirable. Elaborate, and, in our opinion, harmful therapeutic programs, such as lavage of the stomach with silver nitrate solution, have been inaugurated by some enthusiasts as a result of finding evidence of gastritis. Such a formidable diagnostic procedure as gastroscopy will tend to fix the attention of the patient more strongly on the stomach, making psychotherapy more difficult.

On the other hand gastroscopy is an objective method of examination which should help to clarify greatly the whole problem of "soldier's stomach." If used purely from a research point of view it is undoubtedly a valuable procedure provided adequate safeguards to the possible harmful effects are taken.

SUMMARY

1. One hundred and ten combat soldiers with chronic non-ulcer dyspepsia were studied in a Field Hospital in the Fifth Army area in Italy during a seven week period of static warfare. Studies included clinical, roentgenographic, psychiatric and gastroscopic examination. An attempt was made to correlate gastroscopic abnormalities with psychiatric status.

2. Fifty-nine per cent had a normal gastric mucosa. 41 per cent had mild to moderate abnormalities consisting of redness, exudation and edema.

3. There was no correlation between the appearance of the mucosa and the symptomatology, the symptoms being the same whether or not the mucosa was normal.

4. Eighty-four and five-tenths per cent of the total and 75 per cent of those with gastroscopic abnormalities had a psychoneurosis. 15.5% were psychiatrically normal.

5. The clinical study is suggestive that the gastroscopic abnormalities noted (being those of superficial gastritis) represented functional circulatory changes (resulting from nervous tension) rather than the signs of organic disease.

REFERENCES

1. HALSTED, J. A., AND WEINBERG, H.: Chronic Dyspepsia Among Soldiers in the North African Theater of Operations. A Study of 100 cases in a General Hospital. *Med. Bull., North African Theater of Operations*, 1: 2, 1944.
2. MONTGOMERY, H., SCHINDLER, R., UNDERDAHL, L. O., BUTTS, H. R., AND WALTERS, W.: *Jour. Amer. Med. Assoc.*, 125: 890, 1944.
3. SCHWARTZ, I. R., AND PERLMUTTER, M.: *Gastroenterology*, 6: 21, 1946.
4. SCHINDLER, R.: *Gastroscopy, The Endoscopic Study of Gastric Pathology*. Univ. of Chicago Press, 1937.
5. ANNIS, J. W.: *Gastroenterology*, 2: 85, 1944.
6. BENEDICT, E. B.: *Gastroenterology*, 1: 62, 1943.
7. JONES, C. M.: *Amer. Jour. of Digestive Diseases*, 8: 205, 1941.
8. HALSTED, J. A., AND WEINBERG, H.: *New Eng. Jour. Med.*, 234: 313, 1946.
9. HOWARD, J. T.: *Bulletin U. S. Army Medical Dept.*, pp. 84-87, 1945.
10. PALMER, W. L.: *Jour. Amer. Med. Assoc.*, 119: 1155, 1942.
11. SCHWARTZ, I. R.: *Gastroenterology*, 6: 105, 1946.
12. ROSEN, S. R., HALSTED, J. A., SCHWARTZ, I. R., AND WEINBERG, H.: Psychiatric Study of 110 Soldiers with Chronic Non-Ulcer Dyspepsia in the Fifth Army. To be published.
13. HALSTED, J. A.: The Management of Patients with Gastric Complaints in the Army Area. *Medical Bulletin of the Mediterranean Theater of Operations*, 3: 178, 1945.
14. FITZGIBBON, J. H., AND LONG, G. B.: *Gastroenterology*, 1: 67, 1943.
15. WOLF, S., AND WOLFF, H. G.: *Human Gastric Function*. Oxford University Press, 1943.
16. DAILEY, M. C.: *Am. Jour. of Digestive Diseases*, 12: 53, 1945.
17. BEAUMONT, W.: Experiments and Observations on the Gastric Juice and the Physiology of Digestion, p. 107, 1833.
18. PORTIS, S. A.: *Psychosomatic Medicine*, 6: 71, 1944.
19. SCHINDLER, R.: *Gastroenterology*, 1: 44, 1943.
20. SCHINDLER, R., AND ORTMAYER, M.: *Am. Jour. Digest. Dis.*, 9: 411, (Dec.) 1942.
21. BENEDICT, E. B., AND MALLOR, T. B.: *Surg. Gynec. and Obst.*, 76: 129, 1943.
22. ALEXANDER, F.: *Psych. Med.*, 1: 7, 1939.
23. ROTH, J. A., IVY, A. C., AND ATKINSON, A. J.: *Jour. Amer. Med. Assoc.*, 126: 814, 1944.

CLINICAL FINDINGS IN AMERICAN SOLDIERS RELEASED FROM A GERMAN PRISON CAMP

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INTRODUCTION

Malnutrition existed in American prisoners released from German camps. That the treatment of these prisoners presented a medical problem is indicated by the issuance of a circular letter, on the 19th of April, 1945, by the Chief Surgeon of the European Theatre of Operations, entitled: "Nutritional Management of Malnourished Recovered Allied Military Personnel." Thirty-four cases of rather severe malnutrition were studied and treated by me personally over a period of four weeks. My findings and treatment constitute the subject matter of this paper.

OBSERVATIONS AND TREATMENT

On the 21st of April, 1945, there were flown from Hanover, Germany, to the 188th (US) General Hospital in England, a number of American prisoners of war who had been freed by the English on April 16th 1945, from two prison camps in the neighborhood of Follingbostel. About two-thirds were "ambulant" but, on arrival, they were just able to drag themselves out of the English ambulances which had transported them from the airport. They were dressed in new uniforms supplied by the British, and when seen coming from the ambulances, in berets and black shoes, it appeared as if some Englishmen had been caught in the American chain of evacuation. A few wore German uniforms, including SS boots, and bore Luger pistols. After being free these men had raided an SS warehouse and barracks which adjoined the camp. Their clothing, during captivity, had consisted only of remnants, and while they shivered and starved, SS men stationed next door were reported well fed and clothed in the best of materials. This lack of clothing may have been a contributing factor to the upper respiratory infections which were prevalent in the group. The period of imprisonment for these men varied from 51 to 445 days. The following stories will describe the treatment accorded these patients and the diet on which they subsisted prior to their release (see table 1).

CASE REPORTS

Case 3: T/Sgt. U. H. B., aged 28, AAF, Height 6'1"; he weighed 230 pounds on the 20th of January 1944 when he bailed out of his airplane over Hamburg, Germany. After the usual interrogations he was sent by rail to a camp near Memel. He was treated fairly well until the 6th of July, 1944. At that time the Memel area was

TABLE 1

CASE NUMBER	DAYS OF CAPTIVITY	HR.	REC	WEIGHT LOSS	DM/DAY	EDEMA OF FEET	ASCITES	SMOOTH TONGUE	ABDOMEN DISTENDED
		%	mill.	lbs.					
1. Spontaneous amputation, toe tips, due to trench foot.....	123	68	3.37	47	61	2+	0	2+	4+
2. Marked diminution in peripheral reflexes and pain in legs.....	129	70	3.44	53	4	0	0	0	0
3. Numerous infected louse bites	89	76	3.81	65	34	1+	0	0	1+
4. Paranychia. Atypical pneumonia with pleural effusion	129	58	2.9	32	6	2+	0	0	2+
5. In prison hospital for pneumonia prior to release.....	283	96	4.6	27	4	0	0	1+	0
6. Transferred to neurosurgical service for gun shot wound of skull—hemiplegia.....	120			30	6	0	0	0	0
7. Numbness of hands. Excessive vomiting on arrival due to over feeding.....	69		4.6	50	11	0	0	1+	4+
8. Extreme wasting of legs. Knee and ankle reflexes very feeble..	117	85	4.3	37	18	0	0	1+	3+
9. Pain in legs. Tongue margins smooth. Serum proteins 4.5..	118	67	3.4	68	*	4+	0	3+	4+
10. Tongue very red. Bloating and belching.....	91	68	3.4	49	9	0	0	0	1+
11. Severe epistaxis. Diarrhea only for a few days.....	423	57	2.9	23	*	0	0	0	0
12. Transferred to surgical service because of wounds.....	96			30	16	0	0	0	0
13. Covered with louse bites.....	88	77	3.9	30	*	0	0	0	0
14. Infected louse bites.....	52	80	4.0	30	20	0	0	0	2+
15. Primary atypical pneumonia.....	239	64	3.2	28	6	0	0	2+	4+
16. A/g ratio 1.3. Total proteins 5. Diffuse nephritis. Urine albumin 4 plus.....	118	67	3.4	70	6	4+	3+	0	2+
17. Transferred to surgical service. Gun shot wound of abdomen..	172			20	15	0	0	0	0
18. Locked in box car five days with 58 others, without water.....	88	71	3.65	48	6	0	0	2+	2+
19. Marked abdominal distension.....	121	68	3.8	35	5	0	0	0	4+
20. Edema to waist.....	122	71	3.5	42	18	4+	0	3+	4+
21. Lobar pneumonia.....	51	77	3.8	25	6	0	0	0	1+
22. Pan sinusitis. Temperature 105°.....	258	70	3.5	35	10	0	0	0	0
23. Liver enlarged. Psychoneurosis, anxiety state.....	89	77	3.8	5	7	3+	2+	0	2+
24. Total serum proteins: 5.2.....	123	67	3.5	20	*	4+	3+	0	0
25. Frostbite of feet.....	259	71	3.5	28	6	1+	0	0	4+

TABLE 1.—*Continued*

CASE NUMBER	DAYS OF CAPTIVITY	IN.	WBC mill-ion	WEIGHT LOSS lbs.	BM/DAY	EDEMA OF FEET	ASCITES	SMOOTH TONGUE	ABDOMEN DISTENDED
26. On four-hundred mile hunger march. Hospitalized in sheep barn.....	191	90	4.8	22	9	0	0	0	2+
27. Interlobar pleural effusion	98	59	2.7	40	20	0	0	0	4+
28. Nasopharyngitis.....	175	80	4.1	38	6	0	0	0	0
29. Pan sinusitis. Serum proteins: 5.8.....	445	65	3.2	50	35	3+	0	0	1+
30. Tender legs and thighs. Keratinization of skin follicles.....	121	67	3.1	74	14	1+	0	0	3+
31. Thrombophlebitis femoral. Hepatic cirrosis.....	122	67	3.3	40	8	2+	3+	2+	4+
32. Transfused 3000 c.c. whole blood. Gastro Intestinal hemorrhage.....	89	22	1.1	50	*	0	0	0	0
33. Lobar pneumonia. Badly louse bitten. Return of childhood asthma.....	179		4.5	58	5	0	0	0	0
34. On four-hundred mile march. Treated in sheep barn hospital for vomiting.....	254	85	4.0	20	*	0	0	0	0

* Not counted.

threatened by the Russians and he, together with two thousand other prisoners, was crowded into a freight steamer and was taken to Swinemunde. On the trip they were given a few buckets of drinking water and the same buckets had to be used as receptacles for urination and defecation. On arrival at Swinemunde they were chained in twos by the wrist and put in box cars. There 20 prisoners and 8 marine cadet guards in each car. When the cars reached Kolburg, the marine cadets were lined with fixed bayonets on either side of a road about two miles in length which led from the depot to the prison camp. Still chained in twos, and chased by police dogs, the prisoners had to run the gauntlet of these 16 year old guards who poked them with their bayonets if they lingered (1). During their stay at Kolburg, food was cut down to two meals a day and consisted of thin soup made from vegetables, potatoes, barley and cabbage. All men lost weight.

On the 20th of February, they were lined up and started on a march of about 400 miles, through rain, snow and cold. On the march all of the men developed a diarrhea. U. B. had as many as 34 bowel movements in one day. Food consisted chiefly of potatoes, tubers and raw wheat, which the men stole from the farms along the route. The guards were grounded Luftwaffe personnel who requisitioned food along the line of march and ate full balanced meals, in view of the starving prisoners. If a prisoner lingered on the wayside, he was beaten with the butt of a guard's rifle.

After thirty days of marching U. B. became extremely ill. He was moved to one of two sheep barns in which 700 men, who had dropped out of the march were treated by one captured English Medical Officer. U. B. was kept in the barn for 22 days and then moved to Stalag 11B at Follingbostel, by boxcar. He was released by the British on the 16th of April, 1945. On arrival at the hospital he weighed 165 lbs., a loss of 65 lbs. His RBC count was 3,810,000, Hb, 76 per cent. He had a sense of fullness after meals and his abdomen was distended and tympanitic. His buttocks were covered with boils which resulted from infected louse bites. Despite these hardships he was cheerful and anxious to get back to duty and to continue to do his part. This spirit was characteristic of the prisoners and was in marked contrast to many other patients seen on the Gastro-Intestinal Section, with functional complaints, who were unable and unwilling to return to duty. It must be remembered that the mental punishment of imprisonment—seeing comrades die of starvation, hopelessness, and brutality of guards—may be worse than lack of food and physical punishment.

Case 4: Pfc. L. C., aged 19, Inf., Height 5'11". He weighed 150 lbs. when captured near St. Vith during the Battle of the Bulge on the 21st of December 1944. He was made to walk twenty-five miles to Prum and from there was taken by box car to Stalag 12A, at Lemberg. There was no heat for the cars, and there were no sanitary facilities except a single pail. The cars were so crowded, each with 58 men, that not all could lie down at the same time. During the trip, which lasted several days, the train was strafed by Allied planes and L. C. sustained a gunshot wound of the left forehead. At Stalag 12A the diet consisted of $\frac{1}{6}$ of a loaf of bread, 2 cups of thin soup, $\frac{1}{10}$ of a can of meat paste, and a cup of tea per day, plus potatoes about once a week. Every two weeks, one Red Cross parcel was distributed among ten men. After a month at Lemberg he was transferred by box car to Stalag 11B. There he was fed only $\frac{1}{4}$ loaf of bread and a piece of cheese daily. In the early weeks of March he developed a diarrhea with 5-6 bowel movements per day, and a transient attack of jaundice. On the 5th of April he began to cough and had chest pain. He was freed the 16th of April, and on arrival at our hospital he weighed 118 lbs.—a loss of 32 lbs. His RBC count was 2,900,000, Hb., 58 per cent. He had marked edema of his feet and paronychia of both middle fingers. He was febrile and had an atypical pneumonia with pleural effusion at his left base. Louse eggs clung to the scrotal hairs. His abdomen was distended.

These men did not suffer the worst treatment of the lot, nor were they the sickest, but represent an average. The accompanying table summarizes the findings in my 34 cases.

The findings common to almost all patients were anemia, weight loss, abdominal distention and weakness. Wasting and weight loss were frightening to the observer. The sunken eyes and thin extremities of some cases are shown in figure 1. These men, four months previously had been fighting men in prime condition. Many complained of pains in the thighs and legs. The

exact cause of these pains is not known but this finding was noted in starved civilians (2). All patients were louse bitten, but only those with numerous infected bites are noted in the table.

Twelve of the patients had pitting edema of the feet and four of these had associated ascites. Anemia, weight loss, and transudation of intracellular fluid can best be explained on the basis of low caloric intake, low protein diet, and poor alimentation due to diarrhea. Plasma proteins measured in six of the cases with edema ranged from 4.5 to 5.5.

Hunger edema has been known for centuries. It was noted particularly in the Balkans during the last war, and Stare (3) found it present in 1945 in 20%



FIG. 1. CASES 4, 31, 9, AND 7. NOTE FACIAL EXPRESSION OF APATHY, SUNKEN EYES AND WASTING OF EXTREMITIES

of Hollanders taken at random in Rotterdam. While beri-beri was a suggested cause of this edema the absence of other signs of this deficiency made hypoproteinemia the most likely etiologic factor. Figure 2 illustrates the average degree of pitting edema of the extremities.

In cases #16 and 31 the ascites was probably aggravated respectively by nephritis and hepatic cirrhosis.

The diarrhea from which all of these patients suffered was at first thought to be a deficiency diarrhea. However, because of the absence of other signs of marked B complex deficiency it was concluded that the diarrhea in most cases had as its basis an irritated digestive tract. This irritation was produced in some cases, by the eating of raw tubers and raw wheat which was stolen from barns along the route of march. The intestinal tract even in well fed individuals is sensitive to the physical state of food. Most of the bowel looseness began on forced marches and not while the soldier was confined in camp; during these marches grass and grains were chewed. Once the gastro-intestinal

gradient was changed the food which was supplied was not of the type to diminish the slope, but to increase it. During the first few days after release these patients were fed the regular English Army Mess ration, the only food available at the time. They were so hungry that they ate large amounts and this tended to increase the intestinal irritability, and resulted in an increase in the number of bowel movements, nausea, vomiting and further abdominal distention. One of the patients developed an incontinence of the anal sphincter and two had ulcerative bowel lesions, as evidenced by blood in their stools.

The objective evidences of avitaminosis were minimal. There was no ascorbic acid deficiency. In nine patients, the tongue margins were smooth. Only in case 9, was there violet discoloration of the tongue, and only in this one case



FIG. 2. CASE 9. HUNGER EDEMA. NOTE PITTING PRODUCED BY THUMB PRESSURE

all observers would agree that a clinical nicotinic acid deficiency existed. The tongue in case 10 was bright red, but neither smooth nor painful. One patient complained of a sore tongue. So many normal persons have a slight smoothness of the tongue margins that in only two of the cases am I willing to admit that there were signs suggesting a lack of nicotinic acid. As to ariboflavinosis—none of the patients had peri-corneal injection, but two had perleche. This was not severe and it could not be definitely attributed to vitamin deficiency.

Five patients had hyperkeratosis. Whether this was due to vitamin A deficiency or was associated with dehydration and lack of bathing facilities cannot be determined. The enlargement of the hair follicles in these cases was striking, and the skin was rough to the touch. English Army men with whom I compared findings and who had seen cases of this type elsewhere stated that a keratitis not differentiable clinically from A avitaminosis can be produced by filth.

The evidence for thiamin deficiency was equivocal. As mentioned previously, several of the patients complained of pains in the legs and thighs. This symptom was most annoying and may have been due to prolonged standing or marching, with associated strain of weakened muscles. Diminished or absent peripheral reflexes were present in a few patients but these may have been normal findings.

Abdominal distention was present in 20 cases. This may have been due to an irritable state of the digestive tract. Most probably it was aggravated by hypoproteinemia, which permitted edema of the bowel wall to occur and which prevented proper absorption of gas and food.

In those cases with extreme weight loss there was slight dorsal kyphosis due to osteoporosis. This condition was noted by other observers in the cases of starved civilians.

The anemia was of the normochromic, or almost hyperchromic type. In cases 11 and 32 the anemia was associated with rather severe hemorrhages from the nose and gastro-intestinal tract, respectively.

On arrival almost all the patients had severe upper respiratory infections; several had pneumonia. There were two severe cases of suppurative sinusitis. These infections were acquired during exposure on forced marches with only tattered clothing for protection. They tended to clear up spontaneously in our warm Nissen Hut Ward.

Only one man was looked on as psychoneurotic. This is remarkable in view of the hardships suffered by these men and in contrast to the large numbers of psychoneurotics seen on the various services of a general hospital.

At first the patients were tired, listless and apathetic (note patient on left of figure 1), but these symptoms soon disappeared with adequate diet.

TREATMENT

The patients were provided with a bland diet and fed in small quantities. At first many vomited if fed a normal quantity of food. Duodenal feeding through a tube as was practiced in some hospitals was not found necessary. Some of the ambulant patients would sneak into the regular mess line after partaking of their small bland meal. Some nurses and Red Cross workers fed candies and fruit to the patients, but this resulted disastrously, with vomiting and increased diarrhea. The purchase of candy and Coca Cola from the Post Exchange had to be prohibited, as these foods were poorly tolerated, and hospital personnel were prohibited from supplementing the diet. The patients, hungry, as they were, had to be convinced of the need for going slow at first, and often one would have to be ordered, under threat of punishment, to eat only small amounts and only of the prescribed foods. The diet was supplemented with multiple vitamin capsules, and in the more severe cases

with liver extract injected intra-muscularly. In some cases the giving of vitamin concentrates by mouth increased the digestive complaints.

Those patients suffering from boils and infected louse bites were treated with penicillin. Those with upper respiratory infections were treated symptomatically except for two who were given sulfadiazine. Transfusions of whole blood were given to all patients with red blood counts below 4,000,000.

RESULTS

In four weeks all patients but two were well on their way to recovery from their malnutritive states. The two cases not responding were numbers 16, suffering from diffuse sub-acute nephritis, and 32, suffering from hepatic cirrhosis and thrombophlebitis of a femoral vein.

SUMMARY

1. Thirty-four released American prisoners were treated at an American general hospital in England.
2. All suffered from malnutrition, most of a severe degree.
3. Hypoproteinemia, anemia, diarrhea, weight loss, and abdominal distention were the common clinical findings. Evidence of avitaminosis was not striking.
4. Respiratory disease and skin infections were the most common complications of the patients state of malnutrition.
5. Most of the soldiers improved rapidly on blood transfusions and small meals of a bland diet supplemented with multivitamin capsules.

REFERENCES

1. Stars and Stripes, May 7, 1945.
2. BURGER, G. C. E., SANDSTRAD, H. R., AND DRUMMOND, SIR JACK: Lancet, 2: 282, 1945.
3. STARE, F. J.: Nutrition Reviews, 3: 225, 1945.

GASTRO-INTESTINAL BLEEDING IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

HISTORICAL REVIEW AND CASE REPORT WITH GASTROSCOPIC FINDINGS AND RUTIN THERAPY

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HISTORICAL REVIEW

Hereditary Hemorrhagic Telangiectasia, although uncommon, is not rare, as evidenced by the recording to date of over one hundred and seventy-five families with more than one thousand members who have suffered from this disease. It is characterized by repeated hemorrhages from groups of abnormally dilated capillaries and veins. Although the condition is inherited as a dominant characteristic, there are reports of affected families in which generations have been free of the disease. The sexes seem to be equally affected and either male or female may transmit the disease to his or her offspring.

The true nature of Hereditary Hemorrhagic Telangiectasia was established in 1901 by the classical report of Osler (1) who separated it from the then large group of hemorrhagic diseases of uncertain and mysterious origin. Osler continued this study (2). Previously in 1896, Rendu (3) reported a case of melena, undoubtedly due to Hereditary Hemorrhagic Telangiectasia. Parkes Weber (4) further clarified this disease in several reports between 1904 and 1939, referring to it as the Osler or Rendu-Osler type of telangiectasia. He differentiated this condition from hemophilia by the absence of sex-linked transmission and by the well-recognized tendency for epistaxis to be the first manifestation. As a result of his work, it has also been known as the Osler-Weber-Rendu disease.

However, as far back as 1865, Babington (5) described clearly an hereditary form of epistaxis, and in 1869 Wilson (6) reported the first case of rectal bleeding from telangiectases. Fox (7) also reported a case of recurrent rectal hemorrhage in 1908; in the same year Phillips (8) described a case with repeated hemorrhage from the pharynx and possibly from the stomach. At this time Hanes (9) described the histology of the lesions, the frequent involvement of the conjunctivae, the nail beds, and the skin, and the characteristic tendency of the lesions to fade after hemorrhage. In 1916 Hutchinson and Oliver (10) reported a patient with recurrent hemorrhage from the rectum and other mucous membranes. All of these reports probably represented cases of Hereditary Hemorrhagic Telangiectasia.

In 1930 Boston (11) added three cases of Hereditary Telangiectasia with

repeated gastric and/or rectal hemorrhages and traced the development of knowledge of this problem. In his own cases he noted a normal blood clotting time and a normal blood platelet count. In addition to commenting on the rather notable absence of any other symptoms suggesting gastro-intestinal disease, he also made the interesting observation that his patients recovered surprisingly rapidly even after rather extensive blood loss. All these observations have since proved to be quite characteristic of the condition. Each of Boston's patients lived past the age of 50 in spite of recurrent gastric hemorrhages since early life. Surgical intervention was deemed necessary in one patient, a man of 32, whose father had also had repeated hematemesis. At operation, the bleeding was discovered coming from a small cluster of abnormal vessels in the stomach. His second patient was a woman of 70 whose sister died at 56 of repeated painless hematemesis, but had inconclusive atypical findings at autopsy.

Fitzhugh (12) reported in 1931 a very interesting patient who had hemoptyses and in whom bronchoscopy revealed telangiectases in the trachea and left bronchus. This same patient was sigmoidoscoped and in the sigmoid colon telangiectases were also seen and biopsied. However, four years later at autopsy, none were seen in either the respiratory or gastro-intestinal tracts. These findings emphasize the later observation of Schuster (13) that individual groups of dilated vessels are not permanent, but rather vary from time to time in their number, size, and tendency to bleed, even to the point of disappearing entirely as first noted by Hanes (9). In another case reported by Hurst and Plummer (14), telangiectases were also seen by sigmoidoscopic examination. The frequency of widespread bleeding from many different sources with hemoptyses, hematemesis, melena, hematuria, and even cerebral vascular accidents was emphasized in Schuster's (13) necropsy report of the finding of telangiectases in the skin, nose, mouth, pharynx, larynx, trachea, stomach, and duodenum.

GASTROSCOPIC REPORTS

Renshaw (15) in 1939 made the first report of the gastroscopic demonstration of telangiectases in the stomach of a typical case. His patient, a man of 44 and without any associated family history, had had intermittent but prolonged periods of progressive weakness beginning in 1927 and relieved in each instance by iron therapy. For five months in 1936 the patient's stools gave a positive benzidine reaction although they were black only when iron was being taken. Bright red blood had been noted in the stools, in the absence of any rectal pain, in 1935 and 1937 and was attributed to the presence of internal hemorrhoids, after sigmoidoscopy. A gastro-intestinal x-ray study in 1937 was interpreted as showing a small spastic pyloric defect. Because of this the

patient was gastroscoped with the finding of a normal fundus and cardia and "some gastritis" of the antrum; however, the visualization was considered unsatisfactory and a second examination was requested. The preliminary emptying of the stomach had yielded gastric juice with 92 units of free HCL and 110 units of total acid.

When first seen by Renshaw in 1939, the patient stated that he had never had any gastro-intestinal symptoms and that his bowel habit had always been a normal one. He gave a definite history of nose bleeds in childhood, and physical examination revealed the presence of multiple, small, brilliant blood red, oval or irregularly circular spots around the mouth, lips, cheeks, and nose; a few were also noted on the nasal septum and turbinates, the nasopharynx, and on the vocal cords. These spots, very few of which were linear or web-like, were not tender and blanched on pressure. Careful examination of the blood elements revealed only a moderate secondary anemia. The stools regularly gave a 2 to 3 plus benzidine reaction. The serology, urine, and icteric index were normal. Anoscopic examination revealed no hemorrhoids.

At this time another gastroscopy was done without difficulty by Renshaw, and good visualization was obtained. The antral mucosa was entirely normal except for eight millet-seed to pin-head sized, bright red, circular, and slightly raised spots on both the angulus and the crest of the antral sphincter muscle. Four more such spots were seen on the lesser curvature of the body of the stomach. Proximal to the angulus, the mucosa was lusterless and granular; these changes were even more marked proximally where six more widely scattered red spots were seen. Renshaw's gastroscopic diagnosis was chronic hypertrophic gastritis of the body and fundus with multiple gastric telangiectases. He felt that the lesions in the stomach looked just like those seen elsewhere on physical examination and were not at all like the gastroscopic appearance of the more commonly seen pigment spots or chronic localized gastric purpura.

Griggs and Baker (16) reported in 1941 a typical case in a man of 69 who had had recurrent bleeding from the nose and skin for 29 years and severe hematemesis twice a year for 19 years up to 1932. Both gastro-intestinal x-ray study and exploratory laparotomy in 1922 had been entirely negative. The patient remained free of bleeding from 1932 to 1940 when he was again seen for hematemesis. At this time another gastro-intestinal x-ray study was negative as was a sigmoidoscopy. This patient was gastroscoped without any abnormal findings. Their other two cases were typical examples of Hereditary Hemorrhagic Telangiectasia with hematemesis, but neither was gastroscoped; one had a negative gastro-intestinal x-ray series. The first patient had a rather obscure family history, but the other two had good family histories. Of much interest was the long history of nosebleeds preceding the gastro-intestinal

bleeding in one patient, whereas in the other the first hematemesis preceded the epistaxes by 4 years, in reversal of the usual order of bleeding in this disease.

A very recent and excellent study was made by Rundles (17) of a patient who had had repeated epistaxes since the age of 14, but had no positive family history. The patient remained well otherwise until he was 35 when a peptic ulcer was demonstrated by x-ray study and then successfully treated medically. On his first hospital admission in 1936, he complained of periumbilical pain, vomiting, black stools, weakness, dyspnea, palpitation, chest pain, and edema. Many small red macules, 1-3 mm. in size, were noted about the lips, tongue, and oral mucous membranes. The stools were markedly positive to the guaiac test and the red blood count was 3.1 million with 26% hemoglobin. A gastro-intestinal x-ray study revealed nothing unusual, but in the chest x-ray a tumor, 4 inches in diameter, was noted in the right middle lobe with a prominent vacular trunk extending to the hilum. The patient was discharged well in five weeks after receiving four transfusions and ferrous sulphate. He remained well five years except for daily epistaxes. In 1942 his periumbilical pain and melena recurred twice, necessitating hospitalization for transfusions and iron therapy.

On readmission in 1944 for melena, many reddish blue slightly raised spots, 1-2 mm. in diameter, were noted on the lips, tongue, and nasal septum with a few on the forearms and finger tips. The previously heard loud continuous murmur, entirely separate from the heart sounds, was still present over the right anterior chest. The spleen was palpable. The stools were guaiac positive and the red blood count 4.5 million with 30% hemoglobin. Again, gastro-intestinal x-ray study was negative, and the chest x-ray unchanged. Sigmoidoscopy was also negative. The patient again responded to iron therapy and his count rose to 5.7 million r.b.c. with 17 grams of hemoglobin in three months. During this admission, bilateral lenticular cataracts were removed without incident.

On this admission a gastroscopy was done by Dr. H. M. Pollard who obtained satisfactory visualization and noted pale mucosa up to the pyloric valve. Several clusters of circular intensely red spots were seen along the lesser curvature, on the anterior wall, and a few were present in the antrum and on the pyloric valve. These telangiectases were sharply circumscribed, about 2-3 mm. in diameter, and level with the mucosal surface. Fresh blood was noted oozing from two or three of these areas.

CASE REPORT

A 50 year old white executive was first seen at the New Haven Hospital in May 1943 because of chronic melena and chronic secondary anemia. Daily mild to moderate epistaxes and daily slight bleeding from the gums had been present since

childhood at which time "dilated veins and red spots" had appeared on his face. He first began to feel below par in 1931 when his friends noted his yellowish sallow pallor, characteristic of the chronic anemia resulting from chronic hemorrhage. His physician then gave him powdered liver and iron. From 1933 to 1939 he had been taking an oral liver preparation every other month with recurrence of the anemia whenever he stopped his medication. Since 1939 oral liver and ferrous sulphate were taken daily to maintain his hemoglobin between 70% and 80%.

No other sources of blood loss were apparent except for two episodes of bleeding from the ear lobes. In recent months repeated nasal cauterization treatments had failed to stop his epistaxes which did not seem profuse enough to account for his anemia. Repeated stool examinations were then made and they revealed the constant presence of occult blood. An upper gastrointestinal x-ray study had then been done without any positive findings. In spite of all this, the patient felt quite well and carried on his full normal activities.

There was no history of bruising easily and any cuts sustained stopped bleeding promptly. No unusual bleeding tendencies were noted at the time of an appendectomy in 1921 and a tonsillectomy in 1935. His past history and system review were otherwise not remarkable except that he was quite likely to have blood streaked sputum during upper respiratory infections. He had also noted transient palpitation and tachycardia several times a week for over thirty-five years.

The family history revealed that, except for his mother, all the members of his immediate family suffered from frequent nosebleeds. Both his father, who died of pneumonia at 69, and his brother, who is alive and well, had prominent fiery venules on the face and ears. One sister had had the most severe epistaxes in the family and she finally died at 52 of anemia, in spite of repeated transfusions. The patient's mother never had any evidence of the disease and died of a cerebral hemorrhage.

Physical examination revealed a well-developed and well-nourished man with a plethoric facies as a result of a network of small red vessels all over the face, especially on the cheeks. By contrast, his mucous membranes were moderately pale. The telangiectatic networks covered the skin of his face, nose, and ear lobes, while small "cherry angioma" were present on the skin of the trunk and on the mucous membranes of the lips, tongue, and throat. These varied from pin-point size to 1-2 mm. in diameter and were also present on the arms, palms, scalp, eyelids, and in the nose. The liver was enlarged with a firm smooth edge extending three finger breadths below the right costal margin. The tip of the spleen was palpable. No other abnormal findings were present except for what was interpreted as a hemic systolic murmur at the cardiac apex and to the left of the sternum.

The red blood count was 3.5 million with hemoglobin 71% (11 grams), the white blood count 7,600 with a normal differential count, and the reticulocytes 10%. The red blood cells were only slightly basophilic and anisocytotic, and the Price-Jones curve showed a mean cell diameter of 7.85 micra. Red blood cell fragility was normal with hemolysis beginning at .42 and completed at .34, as compared with control readings of .44 and .34 respectively. The platelets numbered 308,200 per cu. mm., bleeding time was 2 minutes, clotting time 4 minutes and 55 seconds, and

the prothrombin time was 11 seconds just as in the control. The N.P.N. was 33 mg. % and the serum proteins were 6.41 grams % with albumin 4.72 grams % and globulin 1.69 grams %. The cephalin flocculation test was negative and the icteric index was 6. The Kahn test was negative. The urine was entirely normal showing no evidence of bile, urobilinogen, or blood. However, the stool was tarry with a four plus guaiac reaction.

The diagnosis was Hereditary Hemorrhagic Telangiectasia with probable hemorrhage from the gastro-intestinal tract. The patient was then asked to eat a high protein diet including one pound of steak or liver every day, and a daily ration of ferrous sulphate, 27 grains, was advised. On this regimen he felt stronger and continued his activities. His small epistaxes continued and his stools remained tarry, probably due to the iron, with a 2 to 4 plus guaiac reaction. The liver remained enlarged, but the spleen was no longer palpable. In January 1944 bilateral inguinal herniae were repaired without incident. Reduction of the ferrous sulphate to 18 grains per day left his red blood count unchanged. An increased frequency of tachycardia led to the taking of an electrocardiogram in December 1944, which proved to be normal.

No change in the patient's course took place until July 1945 when, following three days of consuming a large variety of food and much liquor, he felt very weak with moderate diarrhea, tarry as usual, and an elevation in temperature to 101°F by mouth. His red blood count was found to be 2.68 million with 7.5 grams of hemoglobin, his stool guaiac was 4 plus, and he was admitted to the New Haven Hospital on July 7, 1945. The findings on examination were essentially as before except for increased pallor of the mucous membranes, a blood pressure of 160/90, and again a palpable spleen. His reticulocytes, N.P.N., serum proteins, icteric index, cephalin flocculation, and prothrombin time were all essentially as before. A bromsulphalein liver function test was marked by less than 5% retention of the dye in a half hour. The patient's temperature returned to normal in three days and the stool guaiac gradually receded to 1 plus at the time of discharge on July 18, 1945, at which time the blood count was only slightly higher than on admission. During this admission a complete gastro-intestinal x-ray study was made without any positive findings.

Convalescence at home was uneventful with the red blood count rising to 3.3 million and 75% hemoglobin. The patient resumed work until August 17, 1945 when he again felt very weak and passed a reddish black stool. He was readmitted to the hospital the next day with an r.b.c. of 2.0 million and 36% hemoglobin. Now, as before, there were no gastro-intestinal symptoms in contrast to the abdominal distress so often described in these cases as an essential part of the picture. The patient was pale and weak as before. He received daily infusions but nothing by mouth for two days, after which time a bland diet was taken well. In ten days his stools became guaiac negative and he was discharged to convalesce at home on his bland high protein diet and ferrous sulphate. A double contrast barium enema on this admission was negative.

As before, the patient rapidly regained his strength. His red blood count rose to 3.5 million with 12.5 grams of hemoglobin at which level it remained, even though

occult blood soon reappeared in his stools which again constantly gave a 3 to 4 plus guaiac reaction. Trial of vitamins C and K in adequate daily dosage had no apparent beneficial effect on the continued melena, a failure to be expected from the lack of evidence of any deficiency in these substances. Nevertheless, the patient remained active daily in his business without any discomfort or indigestion except for the observation that a rumbling diarrhea was likely to follow the ingestion of large quantities of milk. However, he took his high protein bland diet and 18 grains of ferrous sulphate every day without any distress.

Although his bowel habits had always been normal, he had noted marked constipation just before the two major episodes of gastro-intestinal hemorrhage just described. The first episode of constipation could not be accounted for, but the second resulted from the ingestion of an aluminum hydroxide gel which had been used in the vain hope that its astringent and buffering action might be helpful. Since the last hemorrhage, small nightly doses of mineral oil had been taken to prevent any constipation. In September 1945 the patient was sigmoidoscoped after thorough preparation, and good visualization as high as 25 centimeters revealed only normal mucosa.

At this time it was felt that gastroscopy would be desirable in an effort to clarify the picture. After a hypodermic injection of 75 mg. of demerol hydrochloride, the pharynx and hypopharynx were anesthetized with 2% pontocaine containing 1:50,000 of epinephrine. Preliminary emptying of the stomach by gravity, using a soft Ewald tube, yielded 25 cc. of clear gray mucoid fluid containing a small amount of free hydrochloric acid as evidenced by the slow color change to blue of a piece of Congo Red paper. Many small clots of bright and dark red blood were present in the fluid.

The standard Schindler-Cameron flexible gastroscope was introduced without difficulty and an excellent view of the corpus, antrum, and angulus was obtained. The mucosa everywhere was dark red, but not especially edematous. Peculiar mucosal lesions with fresh blood oozing from some of them were seen scattered everywhere and increasing markedly in number as one went from the cardia, where there were very few, to the antrum where there was a large conglomeration of them. At first glance these lesions looked like superficial mucosal purpuric hemorrhages, 1 to 10 mm. in diameter, some dark red, others a deep bluish black. However, on careful close inspection, the larger ones were seen to have finger-like projections of varying length, interpreted as branching vessels. It seemed clear then that these were ecchymotic-like telangiectases, similar in appearance to those described by Osler (1) in an autopsy on one of his cases. In addition, a few small bright red, raised "cherry angiomas," about 1-2 mm. in diameter, were seen diffusely scattered throughout the stomach; they were identical with the "red spots" on the skin and oral mucous membranes. Along the anterior edge of the angulus there was a large distended blue vein from which large drops of a mucoid brownish fluid were dripping. Figure 1 represents a highly schematic drawing of the gastroscopic picture at "Depth of Introduction I, position 10 o'clock." The artist has reproduced remarkably well the visualized lesions. Several smaller but prominent distended veins were seen just below the cardia on both the anterior wall and the greater curvature.

These findings were interpreted as a conclusive demonstration of the presence of

telangiectasia of the stomach. Since the lesions increased progressively in number from the cardia to the pylorus, it seemed reasonable to assume that they were even more numerous beyond the pylorus in the duodenum and small intestine; this would help explain the chronic melena in the absence of hematemesis. The gastroscopic findings of Renshaw and Pollard indicated the presence of the circumscribed bright red angioma alone in their cases. The author's patient had, in addition, ecchymotic-like telangiectases representing the gastric mucosal equivalent of the vascular networks on his face, nose, and ears.

In spite of the constant presence of a heavy trace of occult blood in his stools, the patient continued to feel quite well and maintained his red blood count at 3.5 to 4.0 million with 12 to 13 grams of hemoglobin. On January 18, 1946 he developed an



FIG. 1. SCHEMATIC DRAWING OF GASTROSCOPIC VIEW AT DEPTH OF INTRODUCTION I, POSITION 10 O'CLOCK

upper respiratory infection with much coughing which persisted as a rather vigorous dry hack. On January 25th he noted that he had dyspnea and tachycardia on exertion and his red blood count on that day was 1.08 million with 5.8 grams hemoglobin. In view of his spontaneous improvement without transfusion during his past two hospital admissions, he was kept at home on his regular regime. He seemed to improve at first with increased strength and a rise in his red blood count to 2.0 million with 7.8 grams of hemoglobin. However from January 29th on he felt weaker, his blood pressure fell from its previous average of $\frac{140-160}{80-90}$ to 130/70, his red blood count fell somewhat, and his mouth temperature rose from normal to 101°F by mouth. In view of all this and especially the patient's repeated observation that a mouth temperature of 101°F usually meant increased bleeding, he was again admitted to the New Haven Hospital on February 6, 1946.

In spite of several reports in the literature that patients with this disorder, particu-

larly those with splenomegaly, tended to have severe transfusion reactions (12), it was felt this risk had to be taken because of the patient's failure to improve. Therefore, on February 7th and again on February 10th, he received 500 cc. of citrated whole blood without any evidence of reactions. His admission r.b.c. of 1.93 million with 5.25 grams of hemoglobin rose to 2.87 million with 8 grams and his reticulocytes rose from an initial low of 2% to 19%. Brisk melena persisted, however, and he also had a severe epistaxis after nasal cautery with silver nitrate on February 13th. He then received further transfusions of 500 cc. of citrated whole blood on February 13th, 15th, and 18th and his r.b.c., which fell to 1.9 million with 6 grams, rose to 3.3 million with 9.5 grams hemoglobin on February 19th, a level maintained until his discharge from the hospital.

During this admission x-ray examination of the chest revealed normal heart and lung findings. The admission prothrombin time was 100%, the bleeding time one minute, and the clotting time $3\frac{1}{2}$ minutes. The urine was negative.

On February 19th the patient was started on rutin, 40 mg. t.i.d. orally, a dose suggested by Dr. J. Q. Griffith, Jr. through whose courtesy the rutin was obtained. Although rutin is not a new drug, having been known for more than a century, its medical application is the result of recent investigation (18) which has shown that rutin appears to have the property of decreasing abnormal capillary fragility. It is similar in action and in chemical structure to vitamin P, first reported in 1936 (19) as a substance, other than vitamin C, which controls hemorrhage in man. In 1939 Scarborough (20) presented evidence from experiments on human subjects to prove the existence of a factor decreasing capillary fragility, this factor being vitamin P. He demonstrated (21) clear cut vitamin P deficiency in man and distinguished between the spontaneous gross hemorrhage of scurvy and the spontaneous petechial hemorrhage of vitamin P deficiency. Apparently the same properties are true of rutin which, like vitamin P, is a flavone glucoside.

It seemed to the author that rutin might well be effective in Hereditary Familial Telangiectasia because of the histological structure of the telangiectases, described by Stock (22) as showing an increased number of dilated vessels with greatly thinned walls and covering tissues, permitting hemorrhage from trivial causes. Dr. Griffith (23) knew of only one other patient with this condition to whom it had been given; this patient had a normal capillary fragility and was not benefited by the rutin. A remarkable change in the character of the author's patient's bleeding was noted within 24 hours after starting him on rutin. His daily epistaxes and bleeding from the gums ceased for the first time since childhood and they have not recurred to the time of this writing.

It does not seem likely that this striking cessation of nose and gum bleeding occurred as a result of the known tendency for the individual groups of dilated vessels to vary from time to time in their number, size, and tendency to bleed even to the point of disappearing entirely (13). Certainly the lesions were still present in the nose and on the gums. Bean (24) felt that the lesions do not disappear spontaneously and can always be found except when they fade with the profound anemia which follows hemorrhage.

After February 21st the rutin was cut to 20 mg. t.i.d. However, occult blood persisted in the stools with a 3 to 4 plus guaiac, a finding to be expected in view of the undoubtedly large number of lesions subject to constant trauma in the gastro-intestinal tract. The patient was discharged on February 23rd to convalesce at home on his high protein bland diet with rutin, 20 mg. t.i.d., and ferrous sulphate, grains 6 t.i.d. p.c.; the iron was later given in the form of ferrous gluconate, grains 10 t.i.d. p.c. The occult blood in his stool fell to a slight trace (guaiac 1 plus) on February 26th and disappeared on March 9th. Since then the guaiac reaction of the stool has varied from 0 to 1 plus. The patient's r.b.c. has risen gradually to 4.16 with 12 grams hemoglobin, and the patient returned to work in mid-March feeling better than ever, physically and psychologically.

COMMENT

This case fulfills in every respect all the criteria for the diagnosis of Hereditary Hemorrhagic Telangiectasia as stated by Goldstein (25) and affirmed by Larrabee and Litman (26): definite hereditary, visible telangiectases with pathologic distribution, and a tendency to bleed from the lesions. As in most of the reported cases, the first manifestations of the disease were epistaxes which began in childhood. Although Bean (24) stated that these childhood nosebleeds often diminish later and then frequently recur in the 3rd and 4th decades when the characteristic skin lesions become prominent, this sequence was not true in the author's patient. His epistaxes and skin lesions appeared in childhood and persisted. Bleeding from the nose is so common because the delicate and easily traumatized telangiectases occur so frequently and profusely on the nasal septum. Hemorrhage from the skin and oral mucous membranes is also quite frequent and is sometimes present exclusively in these areas. Gastro-intestinal hemorrhage usually begins in the fourth decade as in the case reported here.

The gastroscopic findings were most interesting, although they differed from those seen by Renshaw (15) and Pollard (17). However, the lesions seen in the author's case were more like those described at the autopsy performed by Osler (1) in one of his cases where death resulted from carcinoma of the stomach. Osler found a dozen round foci in the gastric mucosa, each 3-4 mm. in diameter. These at first resembled ecchymoses but, on closer inspection, proved to be dilated venules and capillaries. The same ecchymotic-like telangiectases were the most striking finding in the case reported. However, a few of the lesions seen by Renshaw and by Pollard were also seen. The gastric lesions visualized must be assumed to be present also in the small intestine and perhaps even in the proximal colon.

Bean (24) described the basic pathology of these telangiectases as a thinning of the vessel walls, particularly the muscular coat, resulting in a bulging or

ballooning of the wall in a defect which may be rather extensive. The lesions tend to be ubiquitous both internally and externally with a large number of lesions in each patient, rather than isolated groups. He felt that the same pattern of distribution was present as in the glomus body or the arteriovenous anastomosis in the skin. The lesions are especially frequent on the palmar surfaces of the hands and fingers, and usually occur also in the nail beds, lips, ears, tip and dorsum of the tongue, and Kiesselbach's area on the nasal septum. They are also widespread in the nasal mucosa, facial skin, buccal mucosa, floor of the mouth, scalp, conjunctivae, and finger tips. Other common sites, according to Bean, are the ear drums, palate, pharynx, larynx, trachea, esophagus, stomach, intestines, bladder, urethra, and uterus. The telangiectases have even been described in the brain, meninges, liver, spleen, and kidneys.

The typical skin lesion is a purplish red spot, sharply demarcated, which may be elevated or flat. A single arterial vessel may connect with the spot, commonly called a "cherry angioma"; when several branches are visible, the lesion looks like an acquired vascular spider. Osler (1) described three types of lesions: pinpoint spots, a spider form like the spider naevus in liver disease, and a nodular type which may gradually arise in the center of the spider. The patient reported here had all three of these types. The widespread distribution and the nature of the lesions readily explain the characteristic hemorrhagic tendencies in these patients; the resulting problem posed by this constant bleeding is often grave and occasionally insurmountable. The chronic anemia is often severe enough to be incapacitating and a number of fatal hemorrhages have been reported, with an average mortality of 4%.

Although Stock (22) reported that the disease has, in a few instances, been traced through six generations, it has more often been traced through three or four generations, indicating possible self-limitation of the hereditary transmission. However, this apparent tendency to spontaneous disappearance of the disease in succeeding generations is obviously of no help in the handling of the immediate problem presented by the patient suffering from the disease. The very multitude of treatments, advocated or actually tried, has indicated the absence of any specific remedy. The more recently recommended treatments include electrolysis, roentgen ray or radium irradiation, microinjection of sclerosing solutions, and parenteral moccasin venom. In general, none of these measures, either alone or in combination, gives conclusive or lasting results. Therapy, on the whole, has been very difficult and unsatisfactory.

The only medication of proven value has been the administration of oral iron in full and continuous dosage to combat the chronic secondary anemia. An adequate high protein diet is essential to help compensate for the chronic blood loss. In the presence of gastro-intestinal bleeding, a bland diet would

seem desirable in the hope of reducing trauma to the thin-walled vascular lesions. Similarly, increased intra-abdominal vascular congestion brought about by the effort of straining as in constipation or heavy lifting, or by excessive coughing should be avoided, as such increased vascular congestion can only increase the tendency toward bleeding. Where the hemorrhage has been sufficiently severe or prolonged to lead to a critically low red blood count or the danger of circulatory failure, transfusion becomes necessary in spite of the danger of transfusion reactions in these patients, especially in those with splenomegaly (12). However, Griggs and Baker (16) reported one patient with severe epistaxes who required eleven transfusions. The patient here reported had five transfusions, all well taken and without incident.

It seems obvious that prevention or correction of the underlying vascular fault must await the discovery of the basic cause. Rutin therapy may well constitute a beginning step in this direction. Since the basic pathology of the telangiectases is a thinning and bulging of the vessel wall which may be of single endothelial cell thickness, a capillary-like vessel results. Vitamin P seems to be essential in maintaining normal vascular endothelial strength together with improved capillary resistance in various conditions whether of known dietary origin or not (27). In this connection, Rennert (28) briefly mentioned several cases of severe gastric hemorrhage with prompt cessation of the bleeding after vitamin P administration, after all other measures, including vitamin C, had failed. Rutin has been shown to be similar to vitamin P both in structure and action (18). One might well expect therefore a most beneficial effect from the administration of rutin in Hereditary Hemorrhagic Telangiectasia, and such an effect appears to have been obtained in the case here reported.

Only further investigation will determine the apparent specificity of rutin in this condition and others. It seems entirely logical that decreasing the fragility and increasing the strength of the wall of these telangiectases by means of rutin should be effective just as in hemorrhage from increased capillary fragility. Rutin has also the tremendous advantage of being entirely non-toxic from present available data (23). If the present promise of rutin is borne out, a new era in the therapy of Hereditary Hemorrhagic Telangiectasia has arrived. It would also appear that rutin may be of the greatest value in other types of bleeding in which there is increased capillary fragility. From a gastroenterological standpoint, the hemorrhagic type or phase of non-specific ulcerative colitis and enteritis may respond in selected instances to rutin with cessation of the often intractable and occasionally dangerous hemorrhage. Certainly these cases could be expected to develop in the course of their illness a deficiency of the factor maintaining normal capillary resistance.

Further developments in the use of rutin hold great promise in gastroenterology as well as in other fields.

SUMMARY

A typical case of Hereditary Hemorrhagic Telangiectasia is reported with chronic gastro-intestinal bleeding of fifteen years duration. The chronic anemia resulting from the constant blood loss was well controlled with oral iron therapy, even after two episodes of severe gastro-intestinal hemorrhage in 1945. The most recent episode of such hemorrhage seemed destined to result gravely in spite of the previous therapy plus five transfusions. Rutin therapy at this point appeared to effect and maintain a prompt cessation of the grave gastro-intestinal hemorrhage and of the daily nose and gum bleeding which had been present for forty years.

CONCLUSIONS

1. Hereditary Hemorrhagic Telangiectasia should be considered in the differential diagnosis of chronic gastro-intestinal bleeding.
2. Gastroscopy offers an invaluable aid in determining the presence of the characteristic lesions in the stomach, since x-ray examination of the gastro-intestinal tract appears to be of no value in these cases.
3. Rutin therapy may represent the long sought for specific remedy for Hereditary Hemorrhagic Telangiectasia.

REFERENCES

1. OSLER, W.: Bull. Johns Hopkins Hosp., 12: 333, 1901.
2. OSLER, W.: Quart. Jour. Med., 1: 53, 1907.
3. RENDU, M.: Bull. et. Mém. Soc. Méd. d. Hôp. de Paris, 3: 731, 1896.
4. PARKES WEBER, F.: Edinburgh, M. J., 15: 346, 1904; Lancet, 2: 160, 1907; Br. Jour. Derm., 48: 182, 1936; Proc. Royal Soc. Med., 32: 1393, 1939.
5. BABINGTON, B. G.: Lancet, 2: 362, 1865.
6. WILSON: Quoted by Boston (11).
7. FOX, T. C.: Br. Jour. Derm., 20: 145, 1908.
8. PHILLIPS, S.: Proc. Royal Soc. Med., 1: 64, 1908.
9. HANES, F. M.: Bull. Johns Hopkins Hosp., 20: 63, 1909.
10. HUTCHINSON, R., AND OLIVER, W. J.: Quart. Jour. Med., 9: 67, 1916.
11. BOSTON, L. N.: Am. Jour. Med. Sc., 180: 798, 1930.
12. FITZ-HUGH, T.: Am. Jour. Med. Sc., 181: 261, 1931.
13. SCHUSTER, N. H.: Jour. Path. and Bact., 44: 29, 1937.
14. HURST, A. F., AND PLUMMER, N. S.: Guy's Hosp. Rep., 82: 81, 1932.
15. RENSHAW, J. F.: Cleveland Cl. Quart., 6: 226, 1939.
16. GRIGGS, D. E., AND BAKER, M. Q.: Am. J. Dig. Dis., 8: 344, 1941.
17. RUNDLES, R. WAYNE: Am. J. Med. Sc., 210: 76, 1945.
18. GRIFFITH, J. Q. JR., COUCH, J. F., AND LINDAUER, M. A.: Proc. Soc. Exp. Biol. Med., 55: 228, 1944.
19. ARMELTANO, L., BENTSÉTH, A., BÉRES, T., RUSZYNÁK, I., AND SZENT-GIORGYI, A.: Deut. Med. Wochschr., 62: 1326, 1936.

20. SCARBOROUGH, H.: Biochem. Jour., 33: 1400, 1939.
21. SCARBOROUGH, H.: Lancet, 239: 644, 1940.
22. STOCK, M. F.: Arch. Otolaryng., 44: 108, 1944.
23. Personal communication from Dr. J. Q. Griffith, Jr.
24. BEAN, W. B.: Medicine, 24: 243, 1945.
25. GOLDSTEIN, H. I.: Arch. Int. Med., 48: 836, 1931.
26. LARRABEE, R. C., AND LITMAN, D.: New Eng. Jour. Med., 207: 1177, 1932.
27. LINDHEIMER, G. T., HINMAN, M. S., AND HALLIDAY, E. G.: Jour. Am. Diet. Assoc., 18: 503, 1942.
28. RENNERT, M.: Zeitschr. f. Urol., 32: 630, 1938.

THE EFFECTS OF β -DIMETHYLAMINOETHYL BENZILATE HYDROCHLORIDE ON INTESTINAL ACTIVITY

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INTRODUCTION

Attempts at finding antispasmodics with a wider margin of safety and a greater range of therapeutic usefulness than those already on the market led to the synthesis of a large number of organic compounds, some of which proved to be worthy of careful study. β -Dimethylaminoethyl benzilate hydrochloride was one of those highly active compounds, the pharmacologic properties of which were investigated by Lee, Scott, and Chen (1). For short, they employed the serial number HK-141. The data obtained justified the conclusion that this drug possessed the two types of antispasmodic activity; namely, musculotropic and neurotropic. These findings prompted the investigation of the effects of this drug on normal postprandial intestinal activity, and on heightened intestinal activity induced by pilocarpine, physostigmine or prostigmine in trained dogs. We were interested in finding out what influence such an antispasmodic would have on intestinal activity in intact unanesthetized animals.

METHODS

Eight dogs weighing between 8 and 12 kilograms and kept on ordinary kennel diet were used in this study. Each of the dogs had an exteriorized skin-covered intestinal loop, normally continuous with the rest of the intestinal tract, prepared according to the procedure previously described (2, 3).

The animals were trained to lie quietly on a padded table throughout the duration of the experiments. Postprandial intestinal activity was recorded kymographically through the loop by means of an air-tight tambour system as detailed in a previous communication (3). Control records of postprandial intestinal activity were registered before administration of the antispasmodic drug by the various routes; namely, orally, subcutaneously, intramuscularly, or intravenously, after which the recording was continued until the activity of the intestinal tract completely recovered from the effects of the drug. Similarly, control records of intestinal motility were taken before the induction of heightened activity by subcutaneous injection of prostigmine (0.25 mg. total), physostigmine (2 mg. total), or pilocarpine (0.5 mg./kg.), and, at the peak of intestinal activity, β -dimethylaminoethyl benzilate hydrochloride was administered in doses varying from 1 to 75 mg. orally, subcutaneously, intramuscularly, or intravenously, and its effect on intestinal activity was recorded until it wore off.

RESULTS

Before administration of any drugs, control records of intestinal activity were obtained from each of the dogs in order to establish the pattern of activity for each intestinal level from which the loop was made. The administration

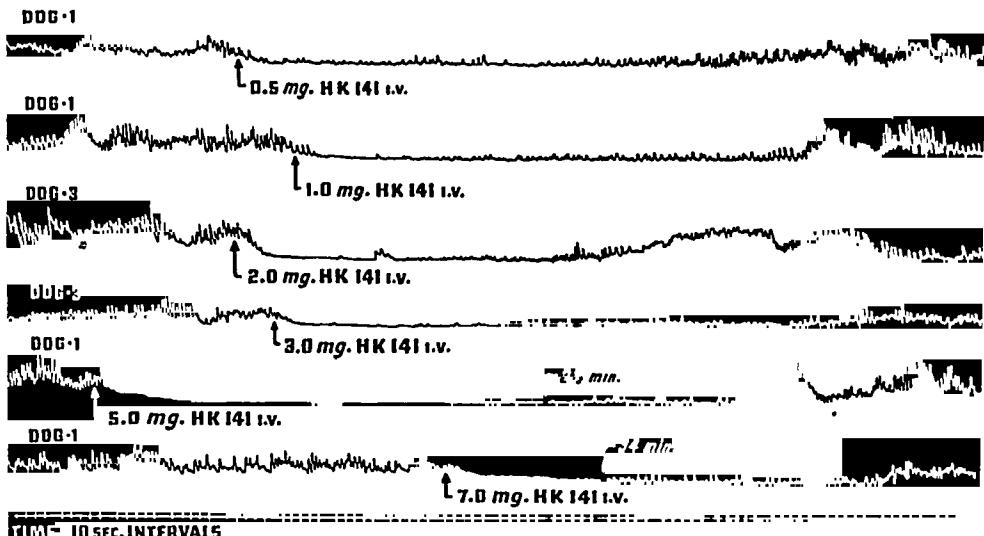


FIG. 1. Kymographic tracings showing the inhibitory effects on postprandial intestinal activity in trained dogs when various doses of β -dimethylaminoethyl benzilate hydrochloride (HK-141) were administered intravenously. The figures above the gap indicate the number of minutes cut out of the tracings. Note the proportionality between dose and duration of effect.

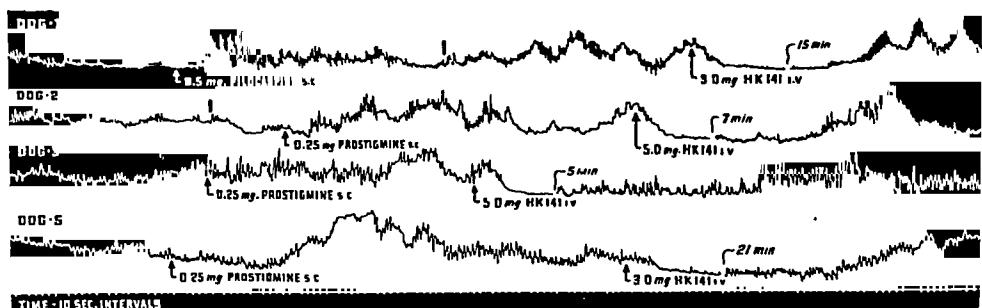


FIG. 2. Kymographic tracings demonstrating the inhibitory effects of β -dimethylaminoethyl benzilate hydrochloride (HK-141) on heightened intestinal activity induced by subcutaneous injection of parasympathomimetic drugs. The figures above the gap indicate the number of minutes cut out of the tracings.

of various doses, ranging from 1 to 75 mg., of β -dimethylaminoethyl benzilate hydrochloride intravenously, intramuscularly, subcutaneously, or orally abolished intestinal activity for periods roughly proportionate with the dose used. The duration of inhibition varied from 0 to 85 minutes depending on the dose and route of administration. The onset of the effect of the drug depended on the route of administration. The intravenous route usually gave an immediate

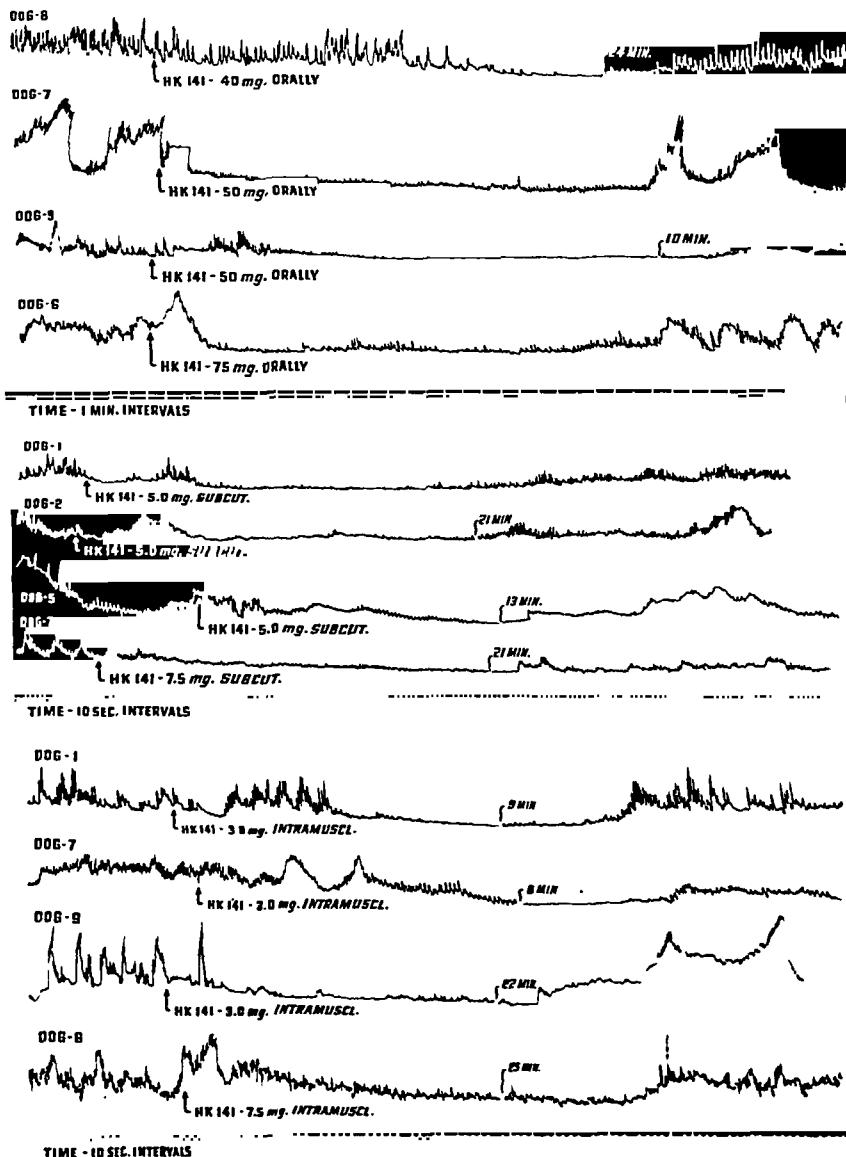


FIG. 3. Kymographic tracings showing the inhibitory effects on postprandial intestinal activity in trained dogs when β -dimethylaminoethyl benzilate hydrochloride was administered orally, subcutaneously or intramuscularly. Note the delay in onset of the effect as compared with that produced by the intravenous route.

effect. When the drug was administered by routes other than the intravenous, some delay occurred before the effect was produced. The delay is attributable to the time consumed by the absorption of the drug. Generally, as the effects

of the drug wore off, rhythmical segmentation movements reappeared before peristalsis.

In figure 1, representative examples of control postprandial intestinal activity and the effects of various doses of β -dimethylaminoethyl benzilate

TABLE 1

Showing the duration of inhibition of intestinal activity in trained dogs upon administration of β -dimethylaminoethyl benzilate hydrochloride (IIK-141)

TOTAL DOSE, mg.	MANNER OF ADMINISTRATION	DURATION (MIN.) OF INHIBITION OF INTESTINAL ACTIVITY				
		Dog no. 1 (jejunum)	Dog no. 2 (jejunum)	Dog no. 3 (upper ileum)	Dog no. 8 (duodenum)	Dog no. 9 (upper ileum)
1	Intravenous	14	7	0	0	12
1	Intravenous	9	7	2	0	14
2	Intravenous	24	13	7	3	23
2	Intravenous	24	10	7	4	19
3	Intravenous	21	13	11	10	17
5	Intravenous	19	25	12	12	19
5	Intravenous	15	18	12	11	33
7	Intravenous	42	50	14	22	46
10	Intravenous	57	55	32	20	43
2	Intravenous*	17	13			
3	Intravenous*	29	6	35		
3	Intravenous*	10		6		
5	Intravenous*	41	12	12		12
3	Intramuscular	14	24	9		
5	Intramuscular	20	22	17	44	
10	Intramuscular*					27
5	Subcutaneous	13	18	8		
7.5	Subcutaneous	18	28	41		24
10	Subcutaneous	29	19	10		23
20	Subcutaneous	85	25	25		38
20	Subcutaneous					23
2.5	Subcutaneous*					6
5	Subcutaneous*				11	
10	Oral				20	32
10	Oral				18	16
15	Oral					21

* Given after induction of heightened intestinal activity by subcutaneous administration of prostigmine, physostigmine, or pilocarpine.

hydrochloride given intravenously are recorded from dogs 1 and 3. Note the immediate cessation of intestinal activity, especially the peristalsis. The figures over the gap in the tracings indicate the number of minutes cut out from the tracing and should be added to the time record to give the total duration of inhibition in these tracings.

Figure 2 presents the initial intestinal activity, the heightened intestinal activity induced by subcutaneous administration of pilocarpine or prostigmine, and the inhibitory effects of the antispasmodic drug on the increased intestinal activity. It is clearly demonstrated that this drug abolished the heightened intestinal activity induced by subcutaneous injection of parasympathomimetic drugs. Again, the figures above the gap in each tracing indicate the number of minutes which should be added to the time record of the duration of inhibition caused by the antispasmodic drug.

Figure 3 gives representative records from a number of animals which were given the drug orally, subcutaneously, or intramuscularly. Note the delay in onset of the inhibitory effect of the antispasmodic drug in contrast with the immediate effect when the intravenous route was used. This delay represents the time taken for the absorption of effective amounts of the drug.

The recorded observations on intestinal activity indicate that the inhibitory effects of this antispasmodic drug on peristaltic activity lasted longer than on the rhythmical segmentation movements.

In table 1 are given the data showing the duration of inhibition in minutes, the dosage, and the manner of administration of β -dimethylaminoethyl benzilate in five dogs with loops prepared from various levels of the intestinal tract. Note the increase in duration of inhibition when large doses of the drug are administered, and also the variation in duration of effect in the different dogs.

SUMMARY AND CONCLUSIONS

A study of the effects of β -dimethylaminoethyl benzilate hydrochloride on postprandial intestinal activity and on heightened intestinal activity induced by subcutaneous injection of parasympathomimetic drugs was made in trained dogs with previously prepared exteriorized skin-covered intestinal loops normally continuous with the rest of the gastrointestinal tract and with circulation and nerve supply intact. Administration of the drug by various routes abolished intestinal activity for durations roughly commensurate with the dose administered. Inhibition of peristalsis lasted longer than inhibition of rhythmical segmentation.

Acknowledgment. The authors are indebted to Mrs. Jacquelyne R. Hannah and Mr. Lowell Sparks for their invaluable assistance in many of the experiments.

REFERENCES

1. LEE, H. M., SCOTT, C. C., AND CHEN K. K.: J. Lab. & Clin. Med., 30: 700, 1945.
2. BIEBL, M.: Klin. Wchnschr., 9: 1674, 1930.
3. WAKIM, K. G., AND MASON, J. W.: Gastroenterol., 4: 92, 1945.

THE EFFECT OF GLUCOSE ON THE MOTILITY OF THE STOMACH AND SMALL INTESTINE

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INTRODUCTION

It has been well established that appreciable amounts of glucose either ingested or given intravenously inhibit gastric motility in both man and lower animals. As early as 1924 Bulato and Carlson (1) showed that intravenous injection of glucose inhibits normal gastric hunger contractions. Since that time numerous workers have confirmed these findings. In 1926 Farrel and Ivy (2) working with the transplanted gastric pouch observed that glucose given intravenously inhibited the motility of the pouch in about 5 minutes.

Quigley, Johnson and Solomon (3) in 1929 found that the presence of carbohydrates in the upper small intestine inhibits gastric motility and a year later Quigley and Templeton (4) suggested that glucose in the duodenum liberates a substance which inhibits gastric hunger movements.

Recently Fenton and Pierce (5) working with rats reported that the emptying rate of the stomach decreased progressively as greater concentrations of glucose were fed.

The majority of the workers who have studied the effect of glucose on gastric motility have used lower animals for their experiments and, moreover, many of the observations reported were made on the effect of glucose on gastric hunger contractions rather than on gastric emptying time. In view of this, it was deemed worthwhile to study carefully the effect of various quantities of glucose on the gastric emptying time in man. During the past fifteen years considerable work has been done in our laboratory on gastric emptying studies in man. Recently (6) the gastric emptying time of 69 normal young male adults was published. These data were helpful in evaluating the experimental results obtained in the work we are now reporting.

Some work has been reported of the influence of glucose on the propulsive motility of the small intestine, but since it is difficult to measure this function of the small intestine, the results have not been as clear cut as might be desired. Further work on the effect of glucose on the motility of this organ was clearly in order.

EXPERIMENTAL

A. Effect of the ingestion of various quantities of glucose on gastric emptying in man.

Methods. Eighteen young males served as subjects. The test meal was eaten about 8:30 a.m. No food had been eaten since the previous evening.

The meal was prepared by boiling 15 gm. of farina in water to a volume of 200 cc.; 100 gm. of barium sulfate were added so the meal could be visualized with the fluoroscope. After the normal gastric emptying time had been determined the effects of the addition of 25, 50 and 75 gm. of glucose were studied in each individual. The glucose was dissolved in the meal at the time of its preparation. The subjects ate the test meal only once a week.

Results. Table 1 shows the results obtained. It will be noted that in each instance the higher the concentration of glucose in the meal the greater the delay in gastric emptying. Twenty-five gm. of glucose produced a prolongation of about 20 per cent above the norm; 50 gm. 39 per cent and 75 gm. 51 per cent. The results were statistically significant.

Discussion. Glucose is capable of causing a delay in gastric emptying by at least two different mechanisms. Each of these will now be considered.

It is known that gastric emptying is influenced by the tonicity of the meal and as our experiments indicate the greater the concentration of glucose the

TABLE 1
Effect of glucose administered with the test meal

	NO. OF SUBJECTS	NO. OF TRIALS	EMPTING TIME	"P"	
			average	hours	
Controls.....	15		3.5	2.22	
25 gm. glucose added.....	7		3.6	2.76	.01
50 gm. glucose added.....	11		4.1	3.09	.01
75 gm. glucose added.....	7		2.7	3.36	.001

* Significant when "P" (according to Fisher) is 0.05 or less.

greater the delay in gastric emptying. These results are in accord with those of other workers.

It was observed by Carnot and Chassevant (7) in 1905 that isotonic solutions of glucose left the stomach faster than hypertonic solutions. They suggested that the diluting action of gastric juice and saliva and mobilization of fluid from the body stores caused the hypertonic solutions in the stomach to become isotonic. Ravdin et al. (8) in 1933 reported that when about 200 cc. of solutions of glucose of varying concentrations, were placed in the stomach of the dog by gastric intubation, an hour later more than 500 cc. were removed. They called attention to the large amounts of water drawn into the stomach and suggested that this mechanism prevented hypertonic solutions from entering the intestine.

It was observed in our laboratory that the size of the meal has a distinct influence on gastric emptying (9). In five subjects a meal twice the size of the control caused a prolongation of the gastric emptying time of 16.83 per cent

and in a meal three times the size of the control 38.33 per cent. The test meal used in the above experiments also consisted of Quaker Farina without, of course, the addition of glucose.

The increased quantity of glucose added to the test meal (25-75 gm.) in the experiments reported in this paper, did not increase the bulk of the meal to any appreciable extent. On the other hand, the addition of glucose caused the meal to be hypertonic and as a result a good deal of fluid entered the stomach. The original meal, therefore, became much larger, but of a watery consistency. After the meal was sufficiently diluted, it probably left the stomach rather rapidly.

It has been known for some time that sugar placed in the upper part of the small intestine in an adequate concentration inhibits gastric motility by the production of enterogastrone. It would seem logical to assume, that with a greater amount of glucose in the stomach, the action of this chalone would be prolonged and gastric motility accordingly inhibited over a longer period.

It is clear then that glucose in adequate concentrations may delay gastric emptying either by the production of enterogastrone or by causing a hypertonicity of the gastric contents. Undoubtedly both of these mechanisms are brought into play.

B. The effect of intravenous glucose on the propulsive motility of the small intestine of dogs.

While there has been a good deal of work reported on the effect of the blood sugar level on the motility of the stomach, very little work has been published on the propulsive motility of the small intestine.

The Russian worker, Belenkov, (10) in 1941 reported that glucose given intravenously inhibited the small intestine of dogs with Thiry-Vella loops and at the same time observed that the motility of the stomach was inhibited. His work is open to criticism, however, since he used only two dogs in his experiments. He pointed out that in postoperative patients that the depressing effects of intestinal motility of anesthesia and preoperative medication would be augmented and prolonged by the use of hypertonic solutions of glucose.

We have reported a considerable amount of work on the propulsive motility of the small intestine during the past three years (11, 12, 13) and it seemed in order to study the effect of intravenous glucose on this function of the small intestine.

Methods. Thirty-seven unanesthetized dogs were used. Essentially Macht's technique was employed to study propulsive motility of the small intestine. Food was withheld from the dogs 24 hours prior to the time they were intubated. Fifty cc. of a charcoal-acacia mixture were given by stomach tube. Three minutes later 1.5 gm. of glucose per kilogram was given intravenously

to 19 dogs. The other 18 animals served as controls and were given an equivalent volume of isotonic saline. A blood sample was withdrawn 25 minutes after intubation for sugar analysis. The Folin-Wu method was used. Five minutes later, that is, 30 minutes after intubation a fatal dose of ether was administered, the small intestine removed and the distance the charcoal mixture had traversed the intestine, measured.

Results. Table 2 gives the results obtained. It will be noted that the average blood sugar of the control dogs was 99 mgm. per 100 cc. blood and that of

TABLE 2
The effect of glucose on the propulsive motility of the small intestine

CONTROL			EXPERIMENTAL		
Length of gut	Distance traversed by charcoal at end of 30 minutes	Blood sugar	Length of gut	Distance traversed by charcoal at end of 30 minutes	Blood sugar
cm.	cm.	mgm. %	cm.	cm.	mgm. %
206	161	74	209	99	296
335	300	103	271	172	198
202	189	99	241	108	296
215	128	78	266	143	292
229	181	87	246	164	312
232	230	98	213	93	300
296	188	99	414	134	152
270	114	113	201	191	304
250	182	132	211	108	306
			222	153	298
210	142	89	183	157	314
185	152	108	214	205	304
189	136	98	252	100	316
239	239	97	235	176	314
236	123	94	282	83	268
280	261	93	317	258	210
211	201	113	267	91	354
289	146	110	208	153	274
296	218	92	321	86	310
Avg. . . 243	183	99	251	141	285

the experimental animals 285 mgm. per cent. In the control dogs the average distance traversed by the charcoal mixture was 183 cms. and in the hyperglycemic group 141 cms. The difference was statistically significant.

Discussion. The data indicate that hyperglycemia produces considerable inhibition of the propulsive motility of the small intestine. It will be noted, however, that there were wide individual variations.

It should be mentioned that because the dogs were untrained and chosen at random, occasionally some difficulty was encountered in making the intra-

venous injections. In some instances due to the animals struggling or to inadequate veins some of the glucose escaped into the surrounding tissues. While the same obtained when normal saline was given to the control dogs, it should be emphasized that glucose is a greater irritant to the tissues.

It is a possibility that the irritation of the peripheral nerves produced by the glucose might have affected gastric emptying and indirectly influenced the distance the charcoal traversed the small intestine. In view, however, of the number of animals used this factor probably is not an important one. In order to overcome this objection entirely, it would be necessary not only to select dogs with adequate veins but also to train them to lie quietly during intravenous medication. Since our experiments were of an acute nature, it was not deemed practicable to train the experimental dogs.

Although the results we obtained were statistically significant, in view of the high grade of hyperglycemia produced, the inhibition of propulsive motility of the small intestine was probably not as great as might be expected. As previously mentioned, Belenkow warned that if glucose is given intravenously to postoperative patients, propulsive motility of the small intestine might be adversely affected, especially since the intestine already was depressed by the anesthetic agent and preoperative medication. Theoretically Belenkow's hypothesis is probably correct, but in view of our work on 19 dogs it is our feeling that glucose alone does not exert an especially powerful influence on propulsive motility of the small intestine. Whether as Belenkow suggests glucose actually enhances the depression of the small intestine caused by other factors, such as, anesthetic agents, preoperative medication and shock accompanying surgical operations is a distinct possibility and should be investigated further. Such a study would be particularly worthwhile since glucose is so widely used following surgical operations.

SUMMARY

The effect on the gastric emptying time of the addition of various quantities of glucose (25, 50 and 75 gm.) to a standard test meal was determined in 19 young adult males. Glucose produced a prolongation of gastric emptying roughly proportional to the amount ingested; 25 gm. produced a prolongation of 20 per cent above the norm; 50 gm. 39 per cent and 75 gm. 51 per cent. These results were statistically significant.

Unanesthetized dogs were given a charcoal-acacia mixture by stomach tube. The experimental animals were then given 1.5 gm. of glucose intravenously per kilogram body-weight and the control animals an equivalent volume of isotonic saline solution. The average blood sugar level of the control dogs was 99 mgm. per cent and that of the experimental 285 mgm. per cent. At

the end of 30 minutes a fatal dose of ether was administered. The charcoal mixture had traversed 183 cms. of the small intestine in the control dogs and in the hyperglycemic group only 141 cms. The difference was statistically significant.

REFERENCES

1. BULATO E., AND CARLSON, A. J.: Am. J. Physiol., 69: 107, 1924.
2. FARREL, J. I., AND IVY, A. C.: Am. J. Physiol., 76: 227, 1926.
3. QUIGLEY, J. P., JOHNSON, V., AND SOLOMON, E. I.: Am. J. Physiol., 90: 89, 1929.
4. QUIGLEY, J. P., AND TEMPLETON, R. D.: Am. J. Physiol., 91: 482, 1930.
5. FENTON, P. F., AND PIERCE, H. B.: Fed. Proceed., Am. Physiol. Soc., 3: 57, 1944.
6. VAN LIERE, E. J., AND NORTHRUP, D. W.: Gastroenterology, 1: 279, 1943.
7. CARNOT, P., AND CHASSEVANT, A.: Compt. Rend. de Soc. Biol., 58: 1064, 1905.
8. RAVDIN, I. S., JOHNSTON, C. G., AND MORRISON, P. J.: Proceed. Soc. Biol. Med., 30: 955, 1933.
9. VAN LIERE, E. J., SLEETH, C. K., AND NORTHRUP, D. W.: Am. J. Physiol., 119: 480, 1937.
10. BELENKOV, N. Yu.: J. Physiol. U.S.S.R., 30: 704, 1941.
11. VAN LIERE, E. J., NORTHRUP, D. W., AND STICKNEY, J. C.: Am. J. Physiol., 141: 462, 1944.
12. VAN LIERE, E. J., NORTHRUP, D. W., AND STICKNEY, J. C.: Am. J. Physiol., 142: 615, 1944.
13. VAN LIERE, E. J., STICKNEY, J. C., AND NORTHRUP, D. W.: Gastroenterology, 5: 37, 1945.

THE EFFECT OF PILOCARPINE ON MUCUS SECRETION BY THE PYLORIC MUCOSA

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INTRODUCTION

Franklin Hollander (11), who recently reviewed the literature on the subject of mucus secretion by the stomach following the injection of pilocarpine, concluded "That there was considerable doubt whether pilocarpine exercises any direct mucus-stimulating action whatever." This conclusion was based on the inconsistency of the reports in the literature since 1899 and on the observations made during experiments performed in his laboratory. Of 27 reports on dogs with some variety of gastric pouch, or gastric and esophageal fistula, 13 gave no sign of evidence for secretion of mucus in response to pilocarpine. In his own experiments, he found that when using a retention technique for collecting gastric secretion, the amount of mucus secreted in response to pilocarpine was much less than that obtained when using a continuous collection technique. The difference was attributed to the stimulation of mucous secretion by mechanical stimulation of the mucosa by the catheter. It was thought that if the mechanical squeezing-out of mucus from the cells, due to the motility stimulated by the drug, could be eliminated, the apparent stimulatory action of pilocarpine on secretion of mucus would be even less (12). As a test of this hypothesis, this investigation was undertaken to measure the secretion of mucus from an everted pyloric pouch in which the mechanical squeezing-out action was reduced to a minimum.

REVIEW OF THE LITERATURE

A pyloric pouch was chosen because it is supposed to secrete mucus almost exclusively. The mucus is derived from the pyloric glands proper and from the mucous cells of the surface epithelium. Although it is generally believed that the vagus innervates the mucus secreting cells (3, 4, 16, 19, 20), there is disagreement as to which of these two types of cells the vagus innervates. Jennings and Florey (13) concluded that the vagus nerve is the secretory nerve of the pyloric glands, because they observed an increase in the volume of secretion, together with histological evidence of a decrease in mucin in the cells of the pyloric glands after vagal stimulation. The adjacent surface epithelial cells, however, showed no evidence of secretory activity as determined by staining with mucicarmine. Babkin (1) believes that most of the secretion arising from vagal stimulation comes from the surface epithelial cells although acknowledging the fact that some of the visible mucus does come from the

mucus forming neck cells. The histological evidence for vagal innervation of the mucus secreting glands of the stomach is meager, in fact, there is no conclusive evidence to be found that nerve endings make a contact with any of the cells in the gastric mucosa.

It has been claimed by Baxter (4) that stimulation of the splanchnic nerves increases the secretion of mucus. This was based on results obtained without an adequate consideration of the spontaneous differences observed in different animals or in the same animal from time to time and without a statistical consideration of the possibility that the differences might be due to random sampling.

In none of the experiments cited above was any precaution taken against mechanical factors arising from the motility of the pouches or various preparations employed; for example, an increase in the volume of secretion might occur as a result of the rubbing of the mucosa of one wall of the stomach against that of the opposite wall. It has been shown that motor activity, even in the absence of other mechanical or chemical stimuli, will cause mucus secretion (5, 6, 10). Others (2, 19) have also observed or discussed the possibility of the causal relationship between the rubbing of mucosal folds upon one another and the discharge of mucus from the glands. Stahnke (16) however, observed the stomach through a gastroscope and claimed that the mucus was actually secreted by the mucosa on vagal stimulation and not merely pressed out from the folds of the mucosa by the movements of the stomach.

The results of many investigators (15, 17, 7, 14, 18) have led to the conclusion that pilocarpine produces a gastric secretion relatively rich in mucus and pepsin and low in free acid and liquid when compared to histamine stimulated juice. As in the experiments with vagal stimulation, no precaution was taken against mechanical factors causing stimulation. Since both vagal stimulation and pilocarpine cause motor activity of the stomach, the failure to eliminate this factor leaves much doubt as to the direct action of pilocarpine on mucus secretion by the stomach. With the evidence at hand, it is not possible to decide whether the increased secretion of mucus frequently noted after administration of pilocarpine is due to direct stimulation of the cells by the drug or to stimulation of the mucus secreting cells by mechanical means secondary to augmentation of motor activity. Since in the gastro-intestinal tract pilocarpine is believed to act only on cells innervated by post-ganglionic cholinergic nerves (8), the lack of knowledge concerning the vagal innervation of the mucus secreting cells adds further doubt to the direct stimulating action of pilocarpine on mucus secreting cells.

The question of whether the cells of the pyloric glands have a parasympathetic innervation in contradistinction to the surface epithelial cells arises from

the work of Jennings and Florey (13). This is of interest because Webster and Komarov (21) assume that soluble mucus comes from the mucus neck cells of the pyloric glands. The soluble mucus content of the secretion obtained by Jennings and Florey was not determined by adding acetic acid to the filtered and neutralized gastric juice as prescribed by Webster and Komarov. Since Hollander (12) measured only the insoluble mucus in his comparative studies, the question regarding the innervation of the several cells and the type of mucus secreted by them remains unanswered.

Other factors affecting the rate of secretion of mucus have been noted. Baxter (4) reported that a "paralytic secretion of mucus" follows double splanchnectomy. Since a vasomotor paralysis follows splanchnectomy, it was considered very probable that this "paralytic secretion" of mucus was a result, at least in part, of a change in vascularity of the gastric mucosa.

METHODS

To accomplish our purpose, pyloric pouches, which were everted so that the mucosa did not rub against anything when the musculature contracted, were made in each of three dogs. No attempt was made to completely denervate the pouches. After from three to five weeks, allowed for recovery post-operatively, the mucus was collected by placing a large glass funnel over the pouch, care being taken that the sides of the funnel were not in contact with the mucosa of the pouch. Control collections were made for several hours and then 5 mg. or approximately 0.4 mg./kg. of pilocarpine hydrochloride was injected subcutaneously. The individual specimens were collected every one-half hour. Mucus was collected for only one hour after the injection of pilocarpine because the effects as measured by salivation, lacrimation, urination and defecation had completely worn off by this time. The latent period of 15 minutes reported by Hollander (12) for gastric secretion from a pouch would come well within this period.

The volume of the insoluble mucus was measured by centrifuging for thirty minutes at 1300 r.p.m. The base was titrated with 0.037 N hydrochloric acid using Topfer's indicator (pH change at 3-4). The reducing substances in terms of glucose were determined by the Somogyi-Schaffer-Hartman method (9), after hydrolysis with 2 N sulfuric acid for three hours.

RESULTS

In addition to the measured results, it was noticed that the mucosa of the pouch changed from a bright red to a purplish red color following the injection of pilocarpine, indicating that vascular changes were occurring. At no time were movements on the surface of the mucosa of the pouch noticed.

In table 1 the volumes for one-half hour periods during the control period and the one-hour period following the injection of pilocarpine are recorded. It will be seen by examining the initial and final one-half hour outputs in the control period that there was a decrease in output in twelve cases, no change in two cases and an increase in four cases. In the one-hour period following the injection of pilocarpine the output of mucus had decreased in all but three

TABLE 1
Volume of fluid collected in one-half hour period in cubic centimeters

TRIALS	CONTROL (TIME IN MINUTES)								AFTER PILOCARPINE	
	30	60	90	120	150	180	210	240	30	60

Dog 1

1	3.9	3.0	3.5	3.6					4.2	3.2
2	5.2	6.3							6.8	6.3
3	7.2	5.2	4.3	4.9					6.3	4.3
4	7.2	5.4	5.1	4.3	4.4				4.3	2.5
5	3.8	3.8	3.4	2.6	2.6	2.6			2.3	2.5
6	3.7	3.2	2.8	2.3	2.4	3.4	2.6	2.1		
7	3.8	4.2	4.2						4.3	2.5
8			3.8	3.5					3.6	2.9
9	3.9	4.9	5.3	5.1					5.0	3.8
Ave.....	4.8	4.5	4.1						4.6	3.5

Dog 2

1	1.0	.95	.65	.65					1.7	1.2
2	1.5	1.5							1.5	1.0
3	1.9	1.6	1.4	1.35					1.2	0.9
4		2.3	2.3	2.3	2.3				2.2	1.4
5	2.6	1.8	1.6	1.5	1.4	1.2			1.3	1.0
6	1.8	1.7	1.7	1.5	1.2	0.9	1.1	1.05	.95	.95
7	2.4	1.5	1.7						1.85	2.4
8			1.4	1.0					.88	.78
9	1.9	2.3	2.4	2.1					1.65	1.11
Ave.....	1.9	1.7	1.7						1.5	1.2

cases, one of which showed no change and two of which showed an increase. In table 2 the averages of the measured quantities obtained from the one hour preceding and following the injection of pilocarpine are shown. From these tables it can be seen that, with no exceptions in the averages, there is a decrease in the total volume, total titratable base and total reducing substances following the injection of pilocarpine. On the other hand the average values for the volume of insoluble mucus showed an increase after the injection of pilocarpine.

When the results are subjected to statistical analysis, however, there is no determination showing a statistically significant difference before and after the injection of pilocarpine.

TABLE 2
Average values obtained before and after the injection of pilocarpine

	DOG I		DOG II		DOG III	
	Trials					
	14		14		6	
	1 hour before	1 hour after	1 hour before	1 hour after	1 hour before	1 hour after
Total volume of mucus (cc.)	8.6	7.6	2.66	2.27	4.3	4.19
Volume of insoluble mucus (cc.)...	.36	.73	.08	.14	.82	1.07
Total glucose (mg.).....	4.09	2.99	3.13	2.30	3.62	3.22
Total base (m. equiv.).....	.203	.139	.087	.063	.122	.104

DISCUSSION

These results bear out Hollander's conclusion "that there is considerable doubt whether pilocarpine exercises any direct mucus-stimulating action whatever." In view of the numerous reports of an increased secretion of mucus following the administration of pilocarpine or vagal stimulation, it can only be said that in none of these previous experiments was the mechanical factor so completely eliminated as in this experiment. Despite the lack of statistical significance there seemed to be a progressive decrease in volume of secretion extending through the control period and into the period following the injection of pilocarpine. This progressive decrease may be a result of changes in blood flow or external stimuli since the activity of the dog in the stocks was less than that in their cages and in the stocks their pouches could not rub against anything. The increase in vascularity as indicated by the change in color of the pouch, however, was of apparently no significance with respect to secretion or its effect was too small to be measured. The change in color of the mucosa from red to a purplish hue suggests that the hyperemia was passive in character. Loss of fluid in the form of urine, saliva, vomitus and feces may have contributed slightly to this apparent progressive decrease in secretion. Because the measurement of insoluble mucus is the determination that Hollander used in his experimental work, these findings have comparative value. Although the average values show an increase in secretion after the injection of pilocarpine, there is no statistically significant difference. While the type of pouch used eliminated rubbing and no gross movements were seen during the experiments, movements of the muscularis mucosae and muscularis

were factors which we had no means of controlling. Possibly such movements resulted in the increase in insoluble mucus which was so frequently obtained. On the other hand, further investigation may show that pilocarpine does actually cause an increase in insoluble mucus by some yet undetermined mechanism. Variations in the output of titratable base may be explained as either the result of a decrease in mucus secretion or an increase in acid secretion, since the operation performed does not absolutely guarantee the absence of parietal cells in the pouch.

Thus, the results indicate that the vagi do not directly stimulate the secretion of mucus by the pyloric glands or the surface epithelial cells of the pyloric mucosa in the dog. The secretion that occurs spontaneously may be the result of a continuous flow of blood or secretagogue and that which occurs in response to mechanical and chemical stimulation may be due to the effect of these stimuli on blood flow, on the cells directly, or on an intrinsic nerve plexus. The role of the sympathetics has not been examined in this study. The work of Jennings and Florey (13) in which they stimulated the vagus and found histological evidence of mucus secretion by the mucus neck cells but not by the surface epithelial cells would seem contradictory to the above considerations. Since they used pouches in which mechanical stimulating factors were not eliminated, and if mechanical factors are involved in mucus secretion, one would expect that the surface epithelial cells would have shown evidence of secretion as well as the neck cells. The interpretation of their evidence is rendered questionable, however, by the histological methods employed, because Florey and Webb (22) using the same methods found a wide discrepancy between the histological evidence of secretion and the macroscopic evidence for the secretion of mucus; i.e., they observed that a volume increase might occur without any change in the mucin granules in the cells.

The possibility that the mucoid neck chief cells of the fundic glands react differently from the pyloric gland cells which they resemble histologically must be excluded before it is concluded that pilocarpine exerts no direct stimulatory action on all types of mucus secreting cells in the stomach; however, there is no evidence to support such an hypothesis.

CONCLUSIONS

Pilocarpine does not stimulate the secretion of mucus by the pyloric mucosa of a dog when precautions are taken to prevent the rubbing together of the folds of the mucus membrane.

REFERENCES

1. BABKIN, B. P.: Secretory Mechanism of the Digestive Glands p. 210, Paul B. Hoeber Inc., New York, 1944.

2. BABKIN, B. P.: Op. cit., p. 211.
3. BABKIN, B. P.: Am. J. Surg., 7: 498, 1929.
4. BAXTER, S. G.: Am. J. Digest. Dis., 1: 36 and 40, 1934.
5. BOLDYREFF, W.: Ergeb. d. Physiol., 11: 120, 1911.
6. CARLSON, A. J.: Am. J. Physiol., 31: 151, 1912.
7. GITLITZ, A. J., AND LEVISON, W.: Am. J. Digest. Dis., 3: 756, 1936.
8. GOODMAN, L., AND GILMAN, A.: The Pharmacological Basis of Therapeutics. p. 389, MacMillan Co., New York, 1941.
9. HAWK, P. B., AND BERGEIM, O.: Practical Physiological Chemistry. Eleventh Edition, Blakiston Co., Philadelphia, 1943.
10. HOELZEL, F.: Am. J. Physiol., 73: 463, 1925.
11. HOLLANDER, F.: Gastroenterology, 2: 201, 1944.
12. HOLLANDER, F.: Am. J. Physiol., 140: 136, 1943.
13. JENNINGS, M. S., AND FLOREY, H.: Quart. J. Exper. Physiol., 30: 329, 1941.
14. LIFSON, N., VARCO, R. L., AND VISSCHER, M. B.: Proc. Soc. Exper. Biol. & Med., 49: 410, 1942.
15. LIGHTSTONE, A.: Proc. Soc. Exper. Biol. Med., 23: 553, 1936.
16. STAHLKE, E.: Arch. Klin. Chir., 132: 1, 1924.
17. TOBY, C. G.: Quart. J. Exper. Physiol., 26: 45, 1936.
18. VINEBERG, A. M., AND BABKIN, B. P.: Am. J. Physiol., 97: 69, 1931.
19. VINEBERG, A. M.: Am. J. Physiol., 96: 363, 1931.
20. WEBSTER, D. R.: Cited by BABKIN, op. cit., p. 211.
21. WEBSTER, D. R., AND KOMAROV, S. A.: J. Biol. Chem., 96: 133, 1932.
22. FLOREY, H., AND WEBB, R. A.: Brit. J. Exper. Path., 12: 286, 1931.

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HEMATEMESIS ASSOCIATED WITH GASTRIC ARTERIOSCLEROSIS

A REVIEW OF THE LITERATURE WITH A CASE REPORT

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Arteriosclerotic changes such as are so frequently seen in the vessels of medium calibre, are rarely encountered in the gastric arteries and their ramifications. A review of the literature reveals only a few cases in which advanced arteriosclerosis of the gastric arteries gave rise to significant pathological lesions in the stomach. The first case of what might be considered as arteriosclerosis of the gastric vessels was reported by Gallard (1) in 1884. He presented two cases of sudden fatal gastric hemorrhage occurring in a twenty-eight and a fifty-one year old man. Post mortem examination revealed small mucosal erosions with aneurysmal dilatation of the small arteries in their base which he interpreted as being due to arteriosclerosis. In 1892, Sacks (2) reported a fatal case of gastric hemorrhage in a seventy-nine year old man with an exposed miliary aneurysm of a small submucosal vessel which he considered to be arteriosclerotic. Markwald (3) described a case of recurrent hematemesis in a man with an arteriosclerotic right coronary artery of the stomach. Ortner (4) reported a case with arteriosclerosis involving the superior coronary gastric artery. Hirschfeld (5) added a case of a thirty-eight year old man with a history of thirteen episodes of gastric hemorrhage over a period of twenty years. Autopsy revealed a perforated aneurysmal artery of the submucosa, distal to which there was necrosis of the stomach mucosa. He also described other aneurysmal and tortuous submucosal arteries.

In 1908, Lewin (6) contributed two cases to the literature occurring in men aged forty and fifty-four. Both were cases of fatal hemorrhage, one hematemesis, the other melena without any previously noted history of bleeding. In both cases there was extensive focal intimal thickening of the gastric arteries with varying degrees of narrowing of the lumen. He did describe black pig-

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ment in the intima (which may have been calcium). Buday (7) in the same year, published a case of sudden fatal hematemesis in a forty year old male with a three year history of bleeding. His descriptions and illustrations of the submucosal vessels were essentially that of advanced arteriosclerosis, viz. marked intimal thickening and calcification.

In 1915, Aihaiia (8) reported a case of a fifty-five year old woman with sudden fatal hematemesis. He noted sclerotic changes in one branch of the left gastric artery with increasing severity of the sclerosis as the artery was followed from the submucosa to the serosa. One branch of this sclerotic and elongated artery bulged into the mucosa with the overlying mucosa of the stomach necrotic. The bleeding was ascribed to rupture of this branch. The next reference in the literature is an article by Zeek and Phair (9) in 1931. They report three cases, all of which showed extensive coronary artery sclerosis of the heart with widespread myocardial damage, in obvious cardiac decompensation. Autopsy revealed ulceration and gangrene of the gastro-enteric tract with sclerosis of the small arteries. In two of their cases ulceration and gangrene involved the stomach. However the main abdominal artery trunks were not markedly sclerotic. In 1932 Reitano (10) published a similar case of a seventy-four year old woman in heart failure. Autopsy revealed fifteen small gastric ulcers lacking the appearance of the typical peptic ulcer in that there were no mucosal or submucosal infiltrations. In the base of the larger ulcers, he found sclerotic vessels.

Buckbinder and Green (11) reported the fourth known case of intra-abdominal but exogastric rupture of a branch of the gastric artery. In their case the right gastric artery was involved. In 1937 Drabig (12) reported two cases of fatal hemorrhage. The first case was a twenty-four year old male with a history of hematemesis of one year duration in which the author found large tortuous submucosal arteries bulging into and thinning the mucosa. In his second case, a female age forty, he noted loss of elastic elements, intimal thickening, and fragmentation of the intimal nuclei. The bleeding was explained in both cases by mucosal ulceration and free bleeding into the gastric lumen from large arteriosclerotic submucosal gastric arteries.

In 1944 Martini (13) attempted to explain epigastric pain in a patient who had hypertrophic gastritis, intermittent claudication, and angina pectoris on the basis of arteriosclerotic gastric vessels. No autopsy was done.

From a review of the literature it appears that arteriosclerosis of the gastric arteries with serious hemorrhage is of sufficient rarity so as to warrant the report of an additional autopsied case.

CASE REPORT

(C. S.; no. 16000.) A male, age forty-four, was first seen in the Consultation Service of The Mount Sinai Hospital in August, 1940 with the following history.

At the age of sixteen he had his first episode of hematemesis. It recurred eighteen months later, this time associated with melena. Since then hematemesis recurred periodically and in all he experienced fifteen episodes of bleeding over a period of thirty years. At the age of twenty, a gastrojejunostomy was done on the assumption that his bleeding may have been due to a peptic ulcer, although there was no radiologic evidence. One year later, because of the persistence of the bleeding, a pyloric resection of the stomach was done. These operations failed to influence the bleeding.

At the age of thirty, he had a febrile episode associated with night sweats lasting for two months. He improved after a ten months' rest in a resort. At the age of thirty-seven, he had hemoptysis and was treated by a private physician who diagnosed tuberculosis involving the right lung. Since then he had intermittent periods of cough. In the ten months prior to August, 1940, he had persistent cough without fever or hemoptysis.

Physical examination in August, 1940 revealed a very thin, slender forty-four year old white male weighing 110 pounds. The positive physical findings were retraction of the supra-clavicular fossae, impairment of resonance in both apices, harsh breath sounds over both upper lobes with amphoric breathing over the right upper lobe, and crepitant rales in the right infraclavicular fossa. The blood pressure was 110/80. The liver and spleen were not palpable and there were no masses or areas of tenderness in the abdomen. Rectal examination was negative.

Laboratory examination revealed the following: Red blood cells 5.9 million, hemoglobin (Sahli) 75%, white cell count 10,000, segmented polys 73%, stasts 6%, lymphocytes 15%, eosinophiles 4%, monocytes 2%, sedimentation time $1\frac{3}{4}$ hours (normal), blood Kahn negative, cholestrol 250 mg.%, esters 160 mg.%, Takata Ara test three plus, galactose tolerance test showed 3.25 grams total excretion, Urine specific gravity 1.022 with a few white cells in the sediment. There was no occult blood in the stool. The B.M.R. was plus 7%, The E.C.G. showed changes indicative of myocardial damage due to coronary atherosclerosis. Barium meal showed the evidence of the previous gastrojejunostomy and gastric resection. X-ray of the chest revealed evidence of tuberculosis involving the apices of both upper lobes. The possibility of activity could not be excluded.

In spite of a thorough search, no cause was found for the repeated episodes of hematemesis. Esophagoscopy and gastroscopy were recommended, but were not done. The patient was returned to the care of his private physician. He died on December 12, 1942, and was sent to this hospital for post-mortem examination.

(P.M. No. K-1026.) The gross description of the stomach was as follows: The prepyloric and pyloric portions of the stomach have been surgically removed. A functioning gastroenterostomy is present, the margins of which are smooth and show no evidence of ulcerations or erosions. The mucosal folds of the fundus are prominent, elsewhere the mucosa is smooth. The color of the mucosa is uniformly reddish grey, and nowhere are there ulcerations, erosions or scars. On the anterior and posterior wall of the fundus near the lesser curvature, numerous tortuous, narrow ridges irregularly traverse the surface of the mucosa and mucosal folds (Fig. 1). On palpation these ridges have a stony hard consistency. They stand out

prominently and on transillumination of the specimen they give the impression of being tortuous arteries. Cross sections of the stomach wall reveal these ridges to



FIG. 1. GASTRIC ARTERIOSCLEROSIS
Note tortuous transverse ridges



FIG. 2. CROSS SECTION OF THE SAME STOMACH AS FIG. 1 SHOWING PIPE-STEM-LIKE VESSELS

be formed by tortuous, gaping, calcified, pipe-stem-like vessels situated in the submucosa and bulging into the mucosa (Fig. 2). Some of these vessels appear to

produce thinning of the overlying mucosa. The lumina of these vessels do not collapse. The cross sectional diameter of the larger vessels measure up to 2 mm.

The cause of death was extensive chronic progressive pulmonary tuberculosis of both lungs with resultant inanition and cachexia.

The anatomical diagnosis was: Chronic progressive pulmonary tuberculosis (bilateral) with multiple cavitation and caseous bronchopneumonia, acute ulcerative tuberculosis of the trachea, larynx, terminal ilium, coecum, and appendix, arteriosclerosis of the submucosal gastric arteries, atherosclerosis of the coronary arteries of the heart (moderate) with moderate narrowing, focal myocardial fibrosis (moderate), atherosclerosis of the aorta (moderate).

Microscopy confirmed the above findings. There was also evidence of arteriosclerotic changes in the vessels of the pancreas, liver, prostate, and heart. The

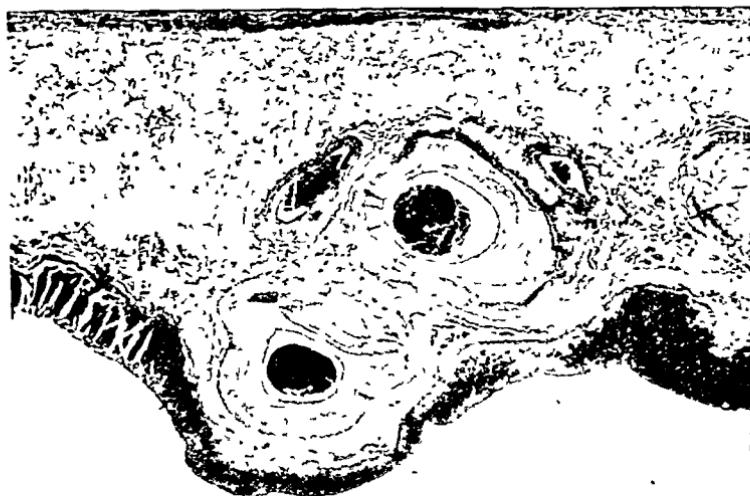


FIG. 3. PHOTOMICROGRAPH OF ARTERIOSCLEROTIC SUBMUCOSAL VESSELS

adrenal arteries showed medial hyalinization and mild arteriosclerosis. The pulmonary vessels revealed endarteritis and endophlebitis.

The arteriosclerosis of the gastric arteries was out of proportion to the changes seen in the vessels of the other organs. The changes seen here were as marked as those seen in advanced coronary artery disease. Sections through the ridges described above revealed the following: The mucosa varied in thickness, the superficial layer showing post-mortem changes and in the deep layer there were focal areas of fibrosis and atrophy of the fundal glands. The muscularis mucosa varied in thickness. The arteries of the submucosa were so tortuous that in each section many loops of the same artery were cut in various planes. The submucosal arteries were unusually large, the average diameter from the external elastic membrane measuring 1.8 mm. These arteries showed extreme intimal thickening (Fig. 3)

produced by loose connective tissue in which were seen numerous Sudanophilic droplets. This fat was for the most part deposited within the tissue spaces but was also seen within a few large macrophages. Frequently segments of the deeper portions of the intima showed calcification, at times impinging upon and narrowing the media. Extension of this calcification into the media was seen. The internal elastic membrane showed striking reduplication, fragmentation and segmental calcification. Nowhere was there actual destruction of the media; only areas of narrowing by compression were seen. The outer elastic lamella and adventitia was without significant change. Whenever the large vessels projected toward the mucosa, the layer of submucosa between the muscularis mucosa and vessel wall was compressed and the loose connective tissue was condensed. Due to the post-mortem changes the capillaries of the mucosa could not be recognized. One area of the mucosa, however, showed superficial hemorrhage.

Random sections including representative parts of the remainder of the stomach showed large submucosal arteries with changes similar to those described above. In addition mild to severe atherosclerosis of the small arteries was seen, occasionally appearing as severe as the large arteries. The serosal arteries occasionally showed severe atherosclerosis.

In summary, this case presents a man who at the age of sixteen experiences hematemesis followed by episodes of severe intermittent gastric bleeding over a period of thirty years, the cause of which was not clinically established. At autopsy, advanced arteriosclerosis of the submucosal branches of the gastric arteries was found. These affected arteries were of extraordinarily large size for submucosal arteries. The cause of death was recurrent pulmonary tuberculosis.

The paucity of similar recorded cases seem to indicate that arteriosclerosis of the gastric arteries is not frequently the cause of severe hematemesis. But in all cases in which severe arteriosclerosis was found, hematemesis had been present. This raises the question as to the frequency of arteriosclerosis of the arteries of the stomach. From a search of the old literature it is difficult to arrive at an estimate of the incidence of arteriosclerosis of the gastric vessels and their branches. Brooks (14) found macroscopic arteriosclerotic lesions in the branches of the coeliac axis in nineteen instances of 368 cases, however he did not specifically investigate the gastric arteries. In a detailed macroscopic examination of the coeliac axis in seven cadavers, Dow (15) found three cases showing atheromatous plaques with consequent narrowing of branch vessels. Schmiedl (16) made a systematic study of the effect of age upon the superior mesenteric artery in 133 bodies. He found that with increasing age there was an increase in the number of cases that showed connective tissue thickening of the intima with deposition of fat and calcium, but all these changes may be absent. He could draw no sharp line between physiological and pathological changes. In the small arteries he noted the changes to be less intense or entirely absent. Hamburger (17) reviewed the literature on gastric arterio-

sclerosis and reported a study of the gastric arteries on ten cadavers. He concluded that neither the age of the patient nor generalized arteriosclerosis bore any relation to the status of the large and submucosal gastric arteries. Six of his cases were interpreted to show definite intimal changes, one mild and one severe. In 1934 Maljatzkaja (21) in a comprehensive study of the arteriosclerotic changes in the abdominal arteries in 85 cases from the ages of 3 to 85 reported relatively little change in the large branches of the gastric coronary and gastroduodenal arteries. The earliest age in which he saw arteriosclerotic changes in these arteries was 42 in contrast to the age of 20 in the coeliac and mesenteric arteries. In the gastroduodenal artery he describes uniform thickening of the intima and elastic lamellation in only 16 cases. These changes were diffuse and not focal. Fifty-five of his cases were over forty years of age. Only when there was severe aortic arteriosclerosis did Maljatzkaja see changes in the gastroduodenal artery.

In passing, one should mention the very controversial subject of arteriosclerosis of the gastric arteries as the cause of gastric ulcers. This would imply that arteriosclerosis of the submucosal arteries is of fairly common occurrence. In 1913 Ophuls (19) emphasized this postulate. Recently Fetterman (20) sectioned numerous areas of thirty surgically resected stomachs for peptic ulcer. He also describes "arteriosclerotic" changes in the intima of the arteries at the base of and about the ulcer. Careful analysis of his tables reveals the presence of a constant inflammation in the areas in which he described artery changes. The majority of pathologists do not accept this postulate and interpret the changes seen in the arteries at the base of and about the ulcer to be due to secondary endarteritis.

A review of the literature on the incidence of arteriosclerosis of the large and submucosal gastric arteries reveals the following. Brooks and Dow did not specifically mention the gastric artery and only by inference can one assume that their description includes the gastric artery. Schmiedl's work is important in that it thoroughly studies a visceral artery. His significant observation is that the small arteries are not as frequently involved, and that he could not draw a sharp line between physiological and pathological changes. Whether this applies to the gastric arteries cannot be inferred. Maljatzkaja showed that the gastroduodenal and coronary artery of the stomach participates very little in the arteriosclerotic process. From the literature the impression is obtained from the above authors that sclerosis of the large gastric arteries are not proportional to the incidence and severity of sclerosis in other arteries and when present is mild in character. This is in accord with the every day impression at the autopsy table.

In order to arrive at the incidence of sclerosis of the submucosal gastric arteries, one hundred consecutive stomachs, obtained at post-mortem in which

adequate sections were available, were studied in this laboratory. Very minimal focal thickening in occasional arteries were seen in a great number of sections. This was not called arteriosclerotic intimal thickening as, in any one given stomach, this thickening was only occasionally seen. In only two cases, age fifty-seven and sixty-five, were there found unquestionable intimal thickening with eccentricity of the lumena. In no way did these changes compare in severity with the case here reported. In thirty-five instances, eleven hypertensives, minimal to mild intimal changes were seen which could be interpreted to be intimal thickening. Calcification was never seen.

The clinical significance of these mild arterial changes must be evaluated. That severe arteriosclerosis as reported in this paper and similar cases in the literature causes hematemesis to the point of being fatal can be definitely stated. Whether mild intimal thickening is clinically significant is questionable. In our survey, the two cases showing moderately severe intimal thickening presented no recorded history or previous gastric symptoms. In the cases of Zeek and Phair (9) and Reitano (10), which showed ulceration and gangrene of the stomach and intestine with small vessel sclerosis, the gangrene did not occur until cardiac failure supervened. Until heart failure occurred these vessels were apparently functionally adequate. It may be presumed that the arteriosclerotic process preceeded the heart failure by many years. Arteriosclerosis of the celiac and mesenteric arteries can be ruled out as a major cause of the gangrene in two of Zeek and Phair's cases as they describe no change in these vessels in one case and only slight change in the other. These cases are unique in that they are the only cases reported in the literature in which one of the contributing cause of gangrene of the stomach and intestine was sclerosis of the small vessels. Thus it may be that even though the small arteries of the stomach and intestine undergo mild to moderate sclerosis, they pre se do not produce clinical manifestations. That an occasional case of hemorrhage is due to arteriosclerosis is probable, but if it does occur it is rare.

The outstanding clinical feature in all of the cases of arteriosclerosis of the gastric arteries reported in the literature is the unexplained repeated gastric hemorrhage occurring from adolescence to senescence. The age of onset in our case was sixteen, the youngest reported age in the literatrue. The oldest reported age was seventy-four (11). In none of the cases was an antemortem diagnosis made. The hematemesis was always recurrent, occurring over a period of days to years. In the case here reported hematemesis recurred fifteen times over a period of thirty years. Such a youthful onset and long duration has never been reported. Contrary to all other reports in the literature, the case here presented died of an intercurrent disease.

The pathological findings in the case presented in this paper were similar to those found by Hirshfeld (5), Lewin (6), Buday (7) and Drabig (13). They

describe large tortuous and extensively arteriosclerotic submucosal arteries. Drabig discusses the unusually large size of the submucosal arteries in his cases and quotes Djorup and Forssell in regard to the normal diameter, 1.0 mm. in the cardia and 0.5 mm. in the fundus of the stomach. The arteries in his cases were within the upper limit of normal.

The diameter of the submucosal gastric arteries in the case here presented were above the upper limits of normal, averaging 1.8 mm. In this case, severe arteriosclerosis with all its classical manifestations is seen in arteries having a diameter ranging from 1.0 mm. to 3.3 mm. The arteriosclerosis seen in these large gastric arteries are morphologically similar to the changes seen in other organ arteries of similar calibre, i.e. the branches of the coronary and cerebral arteries. Normally the arteries of the submucosa of the stomach are considerable smaller and if arteriosclerosis occurs, it is minimal to mild and calcification never occurs. One can speculate that because these severely arteriosclerotic submucosal arteries are abnormally large, the type of arteriosclerosis that develops is similar to the type seen in other arteries of similar calibre.

In the case here presented, the question as to the etiology of the bleeding must be explained. Can it be assumed that the bleeding at the age of sixteen was due to the arteriosclerosis found 30 years later? If this is assumed then we also must assume that this patient had arteriosclerosis severe enough at the age of sixteen to cause bleeding. This is not probable. If Drabig's observations are taken as to the large size of the artery and its close approximation to the surface of the mucosa (also observed in our case) then a small erosion just above the artery can easily open the artery to cause severe hematemesis. In the case here presented we observed fibrosis of the mucosa just above the affected artery which can be taken as evidence of an erosive process occurring at one time. In the later stage the bleeding can be due to rupture of an aneurysmal arteriosclerotic submucosal artery.

In any event, we must conclude that advanced arteriosclerosis with large calibred submucosal gastric arteries is a rare phenomenon and gives rise to recurrent, almost invariably fatal hemorrhage. The onset of the hematemesis can occur at any age, and recur over a period of days to decades. In our case, as in all other cases reported in the literature in which fatal or recurrent hematemesis occurred, severe grades of arteriosclerosis were found in abnormally large gastric arteries. Hematemesis caused by mild degrees of arteriosclerosis of the submucosal arteries is not mentioned in the literature.

SUMMARY AND CONCLUSIONS

1. The literature pertinent to gastric arteriosclerosis is reviewed. There are few reported cases of severe gastric arteriosclerosis.
2. All cases in the literature with severe arteriosclerosis of the gastric

submucosal arteries manifested clinically unexplained repeated gastric hemorrhage occurring from adolescence to senescence.

3. A case of gastric arteriosclerosis with repeated hematemesis is presented.
4. The literature reveals that the gastric arteries are much less frequently involved in the arteriosclerotic process and to a lesser degree.

5. An analysis of the gastric submucosal arteries in 100 stomachs revealed two instances of moderate arteriosclerosis. In these two cases there was no clinical history of gastric complaints. In thirty-five instances, minimal to mild arteriosclerosis was seen, in the submucosal ramification of the gastric arteries. It is doubtful if such arteriosclerosis of the small vessels of the gastro-intestinal tract is per se functionally significant.

6. Attention is called to the fact that Drabig noted the arteriosclerotic submucosal arteries to be of large calibre. The large calibre of the arteries may be the explanation for such severe arteriosclerosis; changes analogous to the sclerosis seen in arteries of similar calibre, i.e. the small branches of the cerebral and coronary arteries.

7. The bleeding may be due either to erosion of these larger arteries abutting upon the mucosa or aneurysmal rupture due to the arteriosclerotic process.

BIBLIOGRAPHY

1. GALLARD, T.: Anéurysmes Miliares de L'estomac donnat lieu à des Hématéméses Mortelles Gazette Des Hospitau, 1884.
2. SACHS, R.: Deutsches Med. Wochenschrift., 20: 1892.
3. MARKWALD.: Zeitschr. Prakt. Artze, 3: 1900.
4. ORTNER, N.: Volksmanns Sammlung Klinischer Vortrage, 347: 1903.
5. HIRSCHFELD, H.: Berl. Klin. Wochenschr., 22: 1904.
6. LEWIN, A. M.: Arch. Verdauungsk., 14: 114, 1908.
7. BUDAY, K. V.: Beitrage z. Path. Anatomie v.z. allg. Path., 44: 327, 1908.
8. AIHAI, S.: Verhandl. d. Jap. Path. Gesellschaft Tokyo, 5: 95, 1915.
9. ZEEK, P., AND PHAIR, J. J.: Amer. J. Med. Sci., 181: 548, 1931.
10. REITANO, R.: Arch. Ital. di. anat. et istal. Path., 3: 377, 1932.
11. BUCKBINDER, J. R., AND GREENE, E. I.: J. A. M. A., 105: 874 (Sept. 14) 1935.
12. DRABIG, F.: Virchows Archiv f. Path. Anat. v. Physiol., 300: 487, 1937.
13. MARTINI, T.: Prensa Med. Argent., 31: 181 (Jan. 26) 1944.
14. BROOKS, H.: Am. J. Med. Sci., 131: 778, 1906.
15. Dow, D. R.: British Medical Journal, 2: 162, 1925.
16. SCHMIEDL, H.: Zeitsch. f. Heilk., 28: 165, 1907.
17. HAMBURGER, W. W.: Deutsches Arch.Klin. Med., 97: 49, 1909.
18. PREVITERA, G.: Arch. Ital. di Anta. et Path., 9: 579, 1939.
19. OPHULS, W.: Arch. Int. Med., 11: 469, 1913.
20. FETTERMAN, G. H.: Arch. Path., 20: 189, 1935.
21. MALJATZKAJA, M. I.: Beitr. z. Path. Anat., 94: 81, 1934.

PUZZLING "NERVOUS STORMS" DUE TO FOOD ALLERGY

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Every busy consultant must see, several times a year, patients with peculiar crisis-like attacks in which it seems that some sort of violent storm goes through the autonomic nervous system and produces a number of alarming symptoms. Nowadays it seems probable that in many of these cases the storm is due to the sudden pouring out into the circulation of some one of the several substances which are formed through nervous action.

Once a physician has had a chance to see a number of these storms, he should begin to recognize them on sight and he should begin firmly, in every case, to refuse to permit even an exploratory laparotomy. The only puzzles that will remain in his mind will be, what is the nature of the underlying sensitization and what is the nature of the trigger mechanism which sets off the attacks?

In some cases the background will clearly be that of an equivalent of insanity or epilepsy or migraine, and the exciting trigger agent will be fatigue or painful emotion. In a few cases the exciting agent will be found to be a drug, such as amidopyrine or phenolphthalein, and in other cases the trap will be sprung by the eating of some food.

The following case report shows what can happen when a person is highly sensitive allergically to some food.

An attractive woman of forty-one was first seen at the Mayo Clinic in 1931 complaining of alarming and prostrating attacks which came every two or three weeks; they laid the woman low for a few hours, and then left her weak and tired for a day or two. The principal symptoms were tachycardia, not paroxysmal in type, with much anxiety and some pain in the left arm and left side of the neck and thorax, great weakness, some dyspnea, marked polyuria, much gurgling and a sense of trembling in the abdomen, perhaps diarrhea, the passage of much flatus, chilliness in hands and feet, pallor of the face, perhaps occipital headache, sometimes a little fever and profuse discharge from the vagina. These spells had been coming for fifteen years or more. During the attacks the systolic blood pressure might go up to 160 mm. Between times the woman's health was good and many careful examinations had shown nothing wrong except a slightly elevated blood pressure. The diagnosis made by most physicians consulted was functional storm of some kind.

About 1934 it occurred to the patient's physicians that the spells might be allergic in origin, and the skin tests then made showed her to be markedly sensitive to cheese. On leaving cheese out of her diet, she improved but she still had some spells. Later the gallbladder was removed but this did not help. Gradually she lost 25 pounds in weight.

When I saw her in 1945, she said there was no question in her mind that the eating

of cheese could bring on a spell but the avoidance of cheese hadn't brought complete relief. She thought that milk was not good for her and hence she did not drink much of it. She also avoided egg. When I tested her skin with the common foods, there was a reaction only to corn. Actually, the patient had been aware since childhood that the eating of corn would cause diarrhea.

The patient was advised to make a greater effort to leave cheese, milk, and all milk products out of her diet. Months later she reported that under this regimen she had had only one attack and had regained her health and most of her lost weight. The one attack experienced had followed the eating of an ice which probably contained some casein. The woman and her husband were very happy over her return to health. They now realize that often before, although she did not willingly eat cheese, she might occasionally get a little of it in a salad dressing or she might get milk or milk products or egg in some cake or other culinary concoction.

CLINICAL PATHOLOGICAL CONFERENCE

A. J. ATKINSON, M. S., M.D.

Records of the Passavant Memorial Hospital (Case 36666), Chicago, Ill.

FIRST ADMISSION

A white woman, aged 35 years, entered the hospital complaining of back pain, and three to four watery stools daily both symptoms of three months duration.

She had been in good health until two years previous to onset of these symptoms. At that time she suffered a severe attack of abdominal pain which was diffuse and lasted over 24 hours. She took a laxative and was relieved shortly thereafter. In the year that followed she had four similar attacks, all of which awakened her from sleep. These attacks were followed by watery stools, pale in color, not of foul odor. In the year preceding admission the attacks continued and began to assume a definite pattern — the pain usually started in the upper left quadrant, radiated to the back and then became diffuse throughout the abdomen. The attacks became increasingly frequent. She had almost constant pain for three weeks preceding admission. This pain was chiefly in her back to the left of the vertebral column in the thoracic and lumbar regions. It was relieved to some extent by heat and by lying on her side with hips and knees flexed. She had a 30 pound weight loss because the ingestion of food, particularly cabbage, chocolate, milk, and fatty foods, produced very severe pain.

During the course of her illness, the patient was examined at two clinics. Gastro-intestinal films showed no pathology. Cholecystography was also negative. Fractional gastric analysis revealed an hyperchlorhydria.

Physical examination revealed an emaciated, young woman lying on her right side with knees and hips flexed, apparently in pain. The buccal mucosa was smooth, velvet-like and gray in color. The tongue was gray and coated. The pharynx was moderately injected. There was moderate splinting of the diaphragm on the left side. The heart and lungs were normal. There were many, superficial, prominent veins on both legs, thighs, and abdomen. A firm, pulsating tumor mass measuring approximately 7 x 22 cm. was palpated in the upper abdomen, extending from the midline to the left anterior axillary line beneath the ribs. The mass was fixed, moving neither with inspiration nor expiration. There was moderate tenderness over the mass and a definite bruit could be heard. Borborygmus was prominent over the entire abdomen except over the tumor mass. Palpation of the uterus produced pain which radiated up the midline.

The blood pressure was 102 systolic and 64 diastolic. The temperature, pulse, and respirations were normal.

Examination of the blood revealed a red cell count of 3,940,000 with a hemoglobin of 12.5 grams and a white cell count of 8,950 with 77 per cent neutrophils. The sedimentation rate was 47 mm. in one hour (Wintrobe). Serum lipase was 1.18 cc. A glucose tolerance test gave a normal curve with no glucosuria.

A gastric analysis showed a fasting free acid of 20 units and a total acid of 30 units.

A roentgenogram of the chest revealed no pathology. Movement of the diaphragm was normal and equal on both sides. A barium study of the colon showed no evidence of a lesion. The splenic flexure was not displaced downward appreciably. The colon appeared atonic and emptied poorly following defecation. A gastro-intestinal series revealed the posterior wall of the stomach to be indented by a large round mass. The pylorus and duodenal bulb appeared normal. The second and third portions of the duodenum showed a marked dilatation. No other abnormality was seen in the digestive tube.

Urinalyses were essentially normal. Routine examination of feces revealed an almost liquid, cream-colored specimen with an occasional red blood cell and 5-6 pus cells, muscle fibers one plus, starch one plus, and fat three plus. Warm stage examinations revealed no parasites or ova. Cultures for *B. typhosus* and *B. dysenteriae* were negative. Specific culture for gas bacillus was negative.

The patient was given 2,000 cc. of 5% glucose and 600 cc. of whole blood and on the 12th day an operation was performed. Her post-operative course was uneventful and she was discharged on the 32nd hospital day.

Differential diagnosis on first admission. With the patient presenting a tumor mass in the upper abdomen we think of *carcinoma of the stomach*, but in this case roentgen examination showed that the lesion was extragastric. *Carcinoma of the colon* was also ruled out by roentgen study.

A tumor of the left lobe of the liver must be considered but against this diagnosis there is an apparent lack of esophageal varices and of metastases elsewhere.

Carcinomatous retro-peritoneal lymph glands, Hodgkin's disease, or leukemic hyperplasias are unlikely because of lack of supportive findings.

Omental tumor, such as a cyst in the lesser omentum, might be thought of but such tumors are usually freely moveable and not likely to indent the stomach.

Aneurysm of the abdominal aorta is very rare in women. There is an expansile pulsation, and there is usually a history of syphilis or arteriosclerosis.

One might also think of such rare diagnoses as *echinococcal cyst, dermoid*

cyst, or *leiomyoma* existing as an exogastric tumor, but these diagnoses would not explain the symptoms associated with this case.

An *enlarged spleen* would not indent the posterior gastric wall, but would be in contact with the anterior abdominal wall, and would be low and lateral to the stomach. An enlarged spleen descends with inspiration.

Pancreatic cysts usually have a tense, elastic consistency, and may transmit a nonexpansile pulsation from the aorta. They frequently are moveable.

An *islet cell adenoma of the pancreas* may give rise to hypoglycemic symptoms. In this case there were no such symptoms, and the glucose tolerance curve was normal. The immobility of this mass, however, makes one think of a pancreatic tumor, because the pancreas lies retro-peritoneally, and the bruit suggests carcinoma of the pancreas. With pancreatic tumor recurring indigestion with intolerance to fats, and pale-colored, loose stools are frequent.

Clinical diagnosis. 1) Pancreatic cyst. 2) Benign tumor of left lobe of liver.

Discussion of findings at surgery. "The mass palpable pre-operatively was immediately palpable posterior to the stomach. The gastro-colic omentum was divided between two clamps and ligated. The solid tumor mass present was then seen to involve the pancreas. It was large, craggy, nodular, and fixed and had broken through the posterior wall of the lesser omental bursa. Here it presented a large (3 x 4 cm.) plaque of hard nodular tissue with reddish, rolled edges, white in the center. This mass was found to be continuous with the pancreas up near its head and to extend down to the Ligament of Treitz where it invaded the posterior layer of the mesocolon. Here it appeared to be necrotic. No liver or lymphatic metastases were found. The first portion of the jejunum was partially compressed by the tumor mass. Due to the large vessels in the mesocolon, it was felt that a posterior gastro-enterostomy was impossible. An anterior gastro-enterostomy was impractical because of the long loop necessary. Believing that the patient would probably die before serious obstruction to the duodenum could occur, the decision was reached not to do the short circuiting procedure. A biopsy was taken from the surface of the tumor presenting in the lesser omental bursa."

Anatomic diagnosis on frozen and paraffin sections from tissue removed at surgery. Carcinoma, transitional cell type. The appearance of the tumor microscopically suggested that it might be a metaplasia of an adenocarcinoma of the pancreas or that it might be secondary to a primary carcinoma of the transitional epithelium of the urinary tract.

SECOND ADMISSION (8 MONTHS LATER)

After discharge the patient was followed in the Out Patient Department. Deep x-ray therapy was started two weeks after surgery (150-200 R.U. three

times weekly). She gained some weight but still complained of intermittent attacks of diarrhea.

The night preceding admission she was awakened suddenly with very severe upper abdominal pain. A physician was called. Morphine failed to give relief. Diarrhea was severe and the patient vomited three times. She was given $7\frac{1}{2}$ grains of sodium amytaL intravenously and slept for one-half hour. The sodium amytaL was repeated and the patient sent to the hospital.

Complete physical examination was not possible at any time. The abdomen was soft but moderately distended. The blood pressure was 80 systolic and 60 diastolic. Temperature was $97.6^{\circ}\text{F}.$, pulse 90, respirations 20. A catheterization yielded 110 cc. of dark amber urine with a specific gravity of 1.034, albumin 0, sugar plus 2.

Examination of the blood showed a red cell count of 2,170,000 with a hemoglobin of 8 grams and a white cell count of 7,450.

Large doses of morphine were given without success and finally sodium amytaL was repeated. The patient became progressively worse; the blood pressure fell to 60 systolic and 40 diastolic; the pulse rose to 130; pallor increased; and she died 24 hours after admission.

Differential diagnosis on second admission. On the second admission to the hospital one must think of hemorrhage because of the fall in blood pressure, increase in pulse rate and pallor, and the decrease in red blood cells and hemoglobin. The hemorrhage could be into the peritoneal cavity or into a hollow viscus. A hemorrhage into the pancreas or retroperitoneally is likely to stop before exsanguination occurs. The pain suggests that there is either an acute pancreatitis or a mesenteric thrombosis. A logical explanation of the terminal event would be that due to carcinoma of the body of the pancreas, thrombosis of the superior mesenteric vein had occurred followed by hemorrhage into the intestine.

Clinical diagnosis. 1) Hemorrhage into the pancreas. 2) Intra-abdominal hemorrhage.

Anatomic diagnosis. 1. Carcinoma simplex of body of pancreas, with fibrosis and necrosis, and adhesions to the stomach, duodenum, splenic flexure of the colon, and the spleen.

2. Stenosis of the portal vein by carcinoma.
3. Thrombosis of the superior mesenteric vein—intestinal branches.
4. Early gangrene of the jejunum and the proximal ileum with hemorrhage into the lumen (1000 cc.).
5. Intraperitoneal hemorrhage 700 cc.).
6. Hypostatic pneumonia-bilateral, early.

DISCUSSION

The immediate cause of death in this patient was mesenteric venous thrombosis with gangrene of the jejunum and upper ileum. The thrombosis resulted from partial occlusion of the portal vein by the pancreatic tumor. The tumor remained local, no metastases being found, with a local complication resulting in death of the patient.



ABRAHAM H. AARON

EDITORIALS

DR. AARON'S PRESIDENTIAL ADDRESS

In this number we publish the thoughtful presidential address of Doctor Aaron. For years he has served the association well and faithfully—with devotion and great friendliness. He possesses that great gift that a few physicians have of a good business sense, and it has been his joy to employ it freely in the handling of the affairs of this association. It is a fortunate group which has as its presiding officer one who is so thoroughly trusted and so well liked. With him in the chair all the society business is sure to be transacted quickly and well.

In the matter of passing on advertising material submitted to this journal he has used much wisdom, and the association is greatly in debt to him for this work.

His suggestions made in the presidential address are thought-producing and should be read with care.

May Doctor Aaron's days be long in the land and in the councils of the American Gastroenterologic Association.

THE USE OF ELIMINATION DIETS AND FOOD DIARIES IN THE DIAGNOSIS OF FOOD ALLERGY

Theoretically, when a person is suffering from a puzzling type of indigestion *every day*, the best way in which to find out if the distress is due to the eating of one or more foods would be to remain for a few days on a definitely nonallergic diet. In trying to devise such a diet Olmsted, Harford and Hampton (1) made a mixture of amino acids, dextrose, salts and vitamins. The idea is a logical one and the method deserves a trial. Today several firms are making mixtures of amino acids, some produced by breaking up casein with the help of acid. The only objection to such digests is their smell and taste which are repulsive to some persons. It is questionable if dextrose should be added to an elimination diet because experience has shown that some allergic persons cannot take it comfortably. It seems to irritate the intestinal mucosa, perhaps in a physical way. Curiously, also, pure vitamins sometimes cause cramps or diarrhea, especially in the case of persons with an allergically sensitive digestive tract. Fortunately, vitamins can easily be left out; a moment's thought will show that they are not needed in a diet which, as Olmsted et al. wisely said, should be discontinued in a week if it fails to abate the patient's distress. Surely no serious avitaminosis is going to develop in that time!

Since the research of Alvarez and Hinshaw (2) showed that in the case of most allergic persons, the gastro-intestinal distress resulting from the eating of an offending food comes within three hours after the ingestion of the material, it is hard to see why an elimination diet should ever be adhered to for more than twenty-four hours when it fails to help, and actually the experience of some workers has led them to give up the experiment in forty-eight hours if no relief comes to the patient in that time.

Persons who suffer with frequently repeated attacks of migraine or eczema will have to stay for a somewhat longer time on an elimination diet, and then it will have to be liberalized so as to make life more worth living. Rowe's (3) diets may be used in such cases.

Practically, a simple elimination diet which usually works well in most cases consists only of oatmeal or rice for breakfast with a little sugar on it, and for luncheon and dinner, a broiled lamb chop with a little rice and some carrots, and a canned pear for dessert. The oatmeal and rice are cooked in water and the lamb is cooked and eaten without condiments. Obviously, during the period of observation no laxative, candy, gum, soft drink or medicine of any kind should be taken. If, after twenty-four hours on the diet the patient's abdominal distress is no better, he should fast for another twenty-four hours, and then if his bowel still burns or aches, or remains full of gas, he can be fairly certain that he is not going to be helped by any diet.

It is strange that so few of the writers on food allergy seem to have seen that different technics are needed in different cases. Some allergists recommend an elimination diet and ignore the food diary method while others advocate a food diary and ignore the elimination diet. Actually, both technics are needed and one cannot easily be used in the place of the other. If a patient gets pain or indigestion every day, then his is a suitable case for trial of an elimination diet, but if his trouble comes only once in two or three weeks, the food diary method is the one to be used.

Actually, before starting an elimination diet the wise physician will say to the patient, "If I were to stop your distress now would the improvement in your comfort be so clear-cut and striking and unusual that you would feel sure it was due to the diet, or would you say, 'Yes, I am better but I cannot say that this means anything because so often I have spells when I am fairly comfortable'?" In such case there is little sense in starting an elimination diet. The procedure is the more hopeless if the patient is a spoiled unobservant person who hasn't enough sense to see the logic of the diet or enough discipline to stick to it faithfully for a day or two.

Actually, the reaction of a woman to the physician's proposal to put her on a narrow elimination diet may be all he needs to make the differential diag-

nosis between scatterbrainness and food allergy. An intelligent person who is suffering and wants relief will immediately see the logic behind the prescription of an elimination diet and will gladly try it out, while a stupid, spoiled, undisciplined or neurotic person who hasn't much wrong with her will immediately start fussing and protesting that she couldn't possibly do without her coffee or her eggs for even one morning. The woman who starts on the diet and then cheats also makes her diagnosis so definitely that the physician need study her case no further.

There is another simple way of differentiating neurosis from allergy and that is by asking the woman who, let us say, states that she is highly sensitive to soft-boiled egg, if she can eat egg with impunity when it is stirred into milk or is cooked into an angel food cake. If she can, her troubles are probably not due to food allergy.

Another good way in which to make sure in a moment that the crises of pain or indigestion complained of are not due to the eating of any *commonly used* food is to ask and find that the spells come only once in a month or two, and that in between, the patient is well. Usually, in such case if the cause of the attack were the eating of some food the patient would soon become aware of the fact and would learn what the food was, because always there would be so close and obvious a relation between cause and effect.

Usually the patient who, without expert help, attempts to keep a food diary gets nowhere because he puts down, not the *unusual* foods eaten, but all the foods. As a result he gathers a mass of data from which he does not know how to extract any information. Often he takes his diary to his physician but that busy man hasn't the time to make the analysis and hence nothing comes of the experiment.

The layman's usual method of trying to find an offending food is to give up one article of diet after another. This usually fails because most allergic persons are sensitive to several foods at a time. They are like the man who tried for years to find the cause of his indigestion after breakfast. Suspecting coffee, he substituted chocolate, but since he was sensitive to chocolate he got worse. He next gave up bacon and substituted sausage but since he was sensitive to the spice and the pork in the sausage he got worse. While testing one food after another, he did not think to eliminate the worst offender, egg, because his nonallergically-trained doctor had remarked that that was invalid's food and hence could never hurt anyone.

Many a physician, when he wants to try an elimination diet, tells the patient to stay for a week or so on nothing but milk, but this usually fails to help because milk stands with onion at the top of the list of the common offenders among foods. One out of four persons is somewhat sensitive to milk, and

hence it is the last food that should be chosen for an elimination diet or as treatment for a person with a puzzling type of indigestion or diarrhea.

In those many cases in which the patient complains of flatulence and abdominal distress during the night or early morning, the simplest and often the most fruitful diagnostic procedure is to have the patient go supperless to bed. If this practically cures him, then he should start trying a new food each evening until he discovers the offending one. In all this sort of work it is essential that the patient keep a record; without it he is not likely to learn anything.

Some may say, "But how about skin tests?" Today even the allergists admit that *in cases of food sensitiveness* skin tests are unreliable and only occasionally give a helpful hint.

W. C. A.

REFERENCES

1. OLMSTED, W. H., HARFORD, C. G., AND HAMPTON, S. F.: Arch. Int. Med., **73**: 341, 1944.
2. ALVAREZ, W. C., AND HINSHAW, H. C.: Proc. Staff Meet., Mayo Clin., **10**: 103, 1935.
3. ROWE, A. H.: Elimination diets and the patient's allergies; a handbook of allergy. Philadelphia, Lea & Febiger, 1941, 264 pp.

GASTRIC TUMORS PRODUCED IN INSECTS BY CUTTING THE NERVE TO THE STOMACH

A curious observation which may some day have important results was reported by Berta Scharrer in the November, 1945, number of the Proceedings for the Society of Experimental Biology and Medicine. She found that in an insect (*Leucophaea maderae*, Orthoptera) section of a sympathetic type of nerve which runs back from the main ganglion in the head to the foregut, resulted, in about 80 per cent of the experiments, in the formation of large rapidly growing tumors in the gastric region. These tumors killed the insects at intervals from ten days to several months after the operation.

No such tumors were found in hundreds of the insects which did not have the nerve cut. Miss Scharrer has already started experiments to see if this phenomenon occurs in any vertebrate.

W. C. A.

WALTER LINCOLN PALMER

THE NEW PRESIDENT

The members of the American Gastroenterological Association are happy to welcome to the Presidency of the organization, Dr. Walter L. Palmer, a genial, friendly and able man.

Born in Evanston, Illinois in 1896, he got his M.D. at Rush Medical College in 1922, his Ph.D. in Physiology at the University of Chicago in 1926. In the years from 1924 to 1926 he was a Resident on the Staff of Cook County Hospital; he was a Seymour Coman Fellow in the Department of Physiology at the University of Chicago from 1924 to 1926. He is attending Physician at the Billings Hospital and Professor of Medicine at the University of Chicago. He is a member of the Association of American Physicians, of the American Society for Clinical Investigation, The Society for Experimental Biology and Medicine, and the Central Society for Clinical Research. He is a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine.

Soon after his graduation from Medical School, he began to publish papers which showed a high degree of research ability, good clear vision and good clinical judgment. Ever since he has been one of the acknowledged leaders in Gastroenterology. It is very fitting that today he is president of the American Gastroenterological Association.

COMMENT

SUPRADIAPHRAGMATIC VAGOTOMY FOR ULCER

Two good studies (1, 2) have been reported recently on the treatment of peptic ulcer by supradiaphragmatic vagotomy. Both reports are in agreement as regards the prompt and complete relief of ulcer symptoms following section of the vagus nerves. Furthermore, both groups of investigators wisely advocate conservatism in evaluating the ultimate rôle that this procedure will play in the control of gastric and duodenal ulcerative disease. This attitude is commendable because, first, there has not as yet been a sufficient number of cases followed for a sufficiently long period of time, and, second, as yet the physiologic basis for this therapy is not fully understood.

Since a clarification of the mechanism of the beneficial effects of vagotomy might add much to our understanding of the onset, healing, and recurrence of peptic ulcer, the physiologic investigations recorded by both the Boston (1) and the Chicago (2) groups are of great importance. They have found that following section of the vagi there occurs a marked decrease in gastric motility and usually a decrease in gastric acidity. It seems reasonable to assume that these alterations account for the observed relief of symptoms and the healing of the ulcers. However, certain discrepancies in these reports remain to be reconciled.

The Boston group of Moore, Chapman, Schulz, and Jones stated that following vagus resection there is a change in free acid values from normal or elevated to zero throughout the greater part of a twenty-four hour period of observation. "Some elevation may be observed an hour or two after the taking of food, but in general the patient goes through the day with no free acid." This is surprising because there is no reason to suspect, on the basis of our present conception of the mechanisms of gastric secretion, that elimination of the vagus supply to the stomach should abolish the gastric secretory response to ingested food. In fact, if, as shown by the Chicago group of Thornton, Storer, and Dragstedt, the usual hospital food in sham feeding tests induced no psychic secretion in the stomachs of seven out of ten patients, later to be operated on, the psychic component of gastric secretion would appear to be relatively unimportant in these patients. One would think, then, that the postoperative gastric secretory response to a meal should be essentially the same as it was before vagotomy. A more likely explanation for the absence of free acid in the Boston patients is to be found in the report that the final gastric emptying time after operation was prolonged up to twenty-four hours. Apparently, in these patients the stomach was never empty of food.

In the uncomplicated cases of ulcer operated on by Dragstedt, the average continuous night secretion after vagotomy was about forty per cent of the average pre-operative level both in volume and in free acidity. Thus, the fasting free acidity, while markedly reduced, was not eliminated. In one patient (case 6) after operation, free acidity was lowered by only 25 per cent, but still it was 30 per cent higher than the average pre-operative figure for all the patients in the series. Furthermore, although this patient showed more than 50 per cent reduction in volume of secretion, he still secreted on an average, 486 c.c. of acid juice during the night. Either this particular patient is a candidate for a recurrence, or the decreased motility is more significant than the decreased secretion in protecting him against further ulceration.

In the report on the Chicago group of cases no mention was made of a delay in gastric emptying, and this seems odd in view of the attention called to this phenomenon by the Boston investigators. They indicated that although the retention of gastric contacts seemed to cause few symptoms, it still could be an occasional cause of a poor clinical result if vagotomy were to come into wider use.

The Chicago investigators reported also on the changes seen following vagotomy in cases of complicated ulcer. There were four patients with obstructing duodenal ulcer, treated by supradiaphragmatic vagotomy plus gastroenterostomy, and five patients with jejunal ulcer, one following previous gastroenterostomy and four following previous gastric resection. The results of vagotomy in the latter group were not so clear-cut. In case 7, for example, there were 566 c.c. of continuous night secretion pre-operatively, with 0 free acid and 21 total; after vagotomy the volume was 361 c.c. with a free acid of 0, and a total acid of 23 units. In case 9 there were 310 c.c. of night secretion with 6 units of free acid and 25 units of total acid, before operation, as compared with 395 c.c. with no free acid and 30 units of total acid, post-operatively. The question arises, can the healing of the jejunal ulcer in these two patients be attributed to the sectioning of the vagi? If so, may not this be construed as evidence that the decreased motility may, in certain cases at least, be more important than decreased acid secretion?

Almost all clinical measurements of gastric secretion must be somewhat misleading and this is due in part to the lack of uniformity in technic, as a result of which it is difficult to compare the findings of different investigators. Thus, in the Boston study, "the standard procedure has been to leave the Levine tube in the stomach for 18 to 48 hours, letting the patient be up and around the ward and allowing him to eat his usual meals without drugs or other artificial stimulation." According to the Chicago report, "at 9 P.M. the stomach was emptied with an Ewald tube. When the returns were clear a

Levine tube was introduced through the nose into the stomach and continuous suction continued until 9 A.M. with the Wangensteen apparatus."

The data of Grimson, as summarized in his discussion of the paper by Thornton et al. (1), showed a striking agreement with the figures of the Chicago investigators in so far as concerns the postoperative reduction of the volume of secretion in the stomach. But in Grimson's series of 18 cases there was considerable individual variation; and five patients showed a moderate reduction in secretion. The gastric secretory response to histamine was described as being less after the operation than before, which is contrary to the findings of the previously cited workers and contrary to what one would expect.

These questions are raised merely to emphasize the need for additional careful observation of the changes which appear following vagotomy, and not to discourage further study of this interesting procedure in the treatment of peptic ulcer. So far the published data indicate that good results are to be expected with immediate relief of symptoms and a marked reduction in gastric motility and perhaps of acidity. Time will tell how permanent these results are to be.

H. M. POLLARD
WILLIAM H. BACHRACH
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REFERENCES

1. MOORE, F. D., CHAPMAN, W. P., SCHULZ, M. D., AND JONES, C. M.: New England J. Med., 234: 241, 1946.
2. THORNTON, T. F., JR., STORER, V. H., AND DRAGSTEDT, L. R.: Journal Am. Med. Ass'n., 130: 764, 1946.

RECENT ADVANCES IN CYTOCHEMISTRY

Microscopic investigations of cells originally revealed only details of structure of the nucleus and cytoplasm. The morphologic and chemical constitution of the nucleus has been explored by geneticists. Among the finer cytoplasmic structures, the mitochondria and the Golgi apparatus have been known for years as permanent elements. These structures are inclusions in a clear hyaline ground-substance of the cell body. The more highly organized cells with secretory functions include also secretory granules. It is obvious that the chemical constitution of these visible portions of the cytoplasm could not be determined by microscopic techniques alone, because even the most refined staining methods are not specific chemical tests. An exception to this is Feulgen's reaction which, like a chemical spot test inside the cell, reveals the presence of thymonucleic acid within the nucleus.

For many years chemists have investigated the chemical constitution of

cells by applying methods of extraction and identification of the isolated substances. They have also contributed to our knowledge of the functions of cells by testing the purified constituents for their biologic activity. Hormones, enzymes, and vitamins isolated from animal and plant cells have thus been investigated. However, exact localization of these chemical components within the cell, and a correlation of vital activity with well defined cell structures could not be accomplished by the organic chemist. This ultimate object of cytology obviously calls for a joint approach through morphology and chemistry. The morphologist must aim at separating separable things (R. R. Bensley (2)) which he can submit to chemical analysis.

Striking advances along these lines have been made in the past ten years by the application of methods which permit of an investigation of cell structures in their natural state unaffected by the influence of fixing agents. R. R. Bensley and his school, using frozen-dried tissues, prepared by the method of Altman-Gersh, submitted this material to fractional extraction with NaCl solution of various concentration and with N/200 ammonia solution. The tissue was studied microscopically after each extraction and the extracted substance examined chemically. The chemical constitution of the mitochondria as phospholipo-nucleoproteins, the presence of glycogen and other submicroscopic particulates was established, and the protein nature of the hyaline ground-substance (Plasmosin and Ellipsin) recognized. A comprehensive review of these investigations can be found in A. Lazarow's article (3) in Vol. X of Biological Symposia dedicated to Professor Bensley which also contains an admirable summary by Bensley (2).

In a series of articles (1940-1945), A. Claude (4) and associates of the Rockefeller Institute have reported the results of their investigations of cytoplasm. By the use of the ultracentrifuge they succeeded in separating mitochondria, secretory granules, and submicroscopic particulates (microsomes), and submitted these portions to chemical analysis, supporting and amplifying the results of the Bensley school. By microspectrography, Caspersson and Schultz (5) have demonstrated the presence of ribosenucleoprotein within the nucleolus and cytoplasm, and have worked out methods for its quantitative determination. The investigations of Claude (4) have localized it within mitochondria, secretory granules, and microsomes. The interparticulate protein substances of the cytoplasm (plasmosin of Bensley) have been purified by Mirsky and Pollister (6) and recognized as desoxyribosenucleoprotein. It is probable that this substance is not of cytoplasmic origin but derived from the nuclear chromatin. The significance of the nucleoproteins for the protein metabolism of normal and carcinomatous cells has been investigated by Caspersson and Santesson (7). (See also the excellent review by Stowell (8)). Rapidly growing cells contain a larger amount of ribosenu-

cleoproteins within their cytoplasm which also show increased basophilia. These cells, as well as those in functional activity, are characterized by large nucleoli rich in ribosenucleic acid.

Enzymatic activity of mitochondria and microsomes, such as succino-dehydrogenase and cytochrome oxydase, has been established by Lazarow and Barron (9) and by Claude (4), 1944, while Emmel (10) has recently suggested the localization of alkaline phosphatase activity within the Golgi apparatus.

In full appreciation of these fundamental investigations, the question must not be evaded as to their significance in the problems of disease. It is obvious that progress in pathology is predicated upon a broad understanding of the normal. The ultimate value for medicine of an expansion of our knowledge of the cell can therefore not be questioned. The question, however, can be centered upon whether the information obtained by this fundamental research can already be utilized by those who are primarily confronted with the structural manifestations of disease. The investigations referred to have been conducted on the highest level of scientific research. They require special investigative skill not easily acquired by the conventionally trained histopathologist. Moreover, the variability of morbid tissue contrasts with the homogeneity of the material used mainly in these studies, not to speak of the artefactual changes encountered in post-mortem material. The application of the methods and results of this fundamental research in the practice of morbid anatomy would therefore be fraught with the danger of serious errors. Yet, the scientific physician, concerned with the morphologic aspect of disease, cannot afford to neglect the revelations of these investigators.

A recent review by Dempsey and Wislocki (11) not only surveys the entire field of cytologic research but also indicates how the results of some of the conventional staining procedures can be interpreted in terms of chemical constitution. Structural details, such as cytoplasmic basophilia or conspicuous nucleoli, have served only as diagnostic criteria in the past. In the light of these basic revelations of cytochemistry they are manifestations of significant alterations in the chemical constitution and function of the cell. The investigations, here reviewed, challenge the curiosity and ingenuity of the histopathologist.

PAUL KLEMPERER.

1. FEULGEN, R., AND ROSENBECK, H.: Hoppe-Seyler's Zeitschrift für phys. Chemie, **135**: 203, 1924.
2. BENSLEY, R. R.: Science, **96**, 389.
3. LAZAROW, A.: Biological Symposia, **10**: 9, 1943. The Jaques Castell Press, Lancaster, Pa.
4. CLAUDE, A.: Transact. N. Y. Acad. of Sciences, Sec. II, Vol. 4, 79, 1941. Science, **97**: 451, 1943.
5. CASPERSSON, T., AND SCHULTZ, J.: Nature, **143**: 602, 1939. Proc. Natl. Ac. of Sc., **26**: 507, 1940.
6. MIRSKY, A. E., AND POLLISTER: Proc. Natl. Ac. of Sc., **28**: 344, 1942.
7. CASPERSSON, T., AND SANTESSON, L.: Act. Rad. Suppl., **46**: 1942.
8. STOWELL, R. E.: Cancer Research, **5**: 283, 1945.

9. LAZAROW, A., AND BARRON: *An. Rec.*, 79: Suppl., 2: 41, 1941.
10. EMMEL, V. M.: *Anat. Rec.*, 91: 39, 1945.
11. DEMPSEY, E. W., AND WISLOCKI, G. B.: *Phys. Rev.*, 26: 1, 1946.

BOOKS—WAR VICTIMS

During the war, the libraries of half the world were destroyed in the fires of battle and in the fires of hate and fanaticism. Where they were spared physical damage, they were impoverished by isolation. There is an urgent need—now—for the printed materials which are basic to the reconstruction of devastated areas and which can help to remove the intellectual blackout of Europe and the Orient.

There is need for a pooling of resources, for coordinated action in order that the devastated libraries of the world may be restocked as far as possible with needed American publications. The American Book Center for War Devastated Libraries, Inc. has come into being to meet this need. It is a program that is born of the combined interest of library and educational organizations, of government agencies, and of many other official and non-official bodies in the United States.

The American Book Center is collecting and is shipping abroad scholarly books and periodicals which will be useful in research and necessary in the physical, economic, social and industrial rehabilitation and reconstruction of Europe and the Far East.

The Center cannot purchase books and periodicals; it must depend upon gifts from individuals, institutions, and organizations. Each state will be organized to participate in the program through the leadership of a state chairman. Other chairmen will organize interest in the principal subject fields. Cooperation with these leaders or direct individual contributions are welcomed.

What is needed: Shipping facilities are precious and demand that all materials be carefully selected. Emphasis is placed upon publications issued during the past decade, upon scholarly books which are important contributions to their fields, upon periodicals (even incomplete volumes) of significance, upon fiction and non-fiction of distinction. All subjects—history, the social sciences, music, fine arts, literature, and especially the sciences and technologies—are wanted.

What is not needed: Textbooks, out-dated monographs, recreational reading, books for children and young people, light fiction, materials of purely local interest, popular magazines such as *Time*, *Life*, *National Geographic*, etc., popular non-fiction of little enduring significance such as Gunther's *Inside Europe*, Haliburton's *Royal Road to Romance*, etc. Only carefully selected

federal and local documents are needed, and donors are requested to write directly to the Center with regard to specific documents.

How to ship: All shipments should be sent PREPAID via the cheapest means of transportation to The American Book Center, C/O The Library of Congress, Washington 25, D. C. Although the Center hopes that donors will assume the costs of transportation of their materials to Washington, when this is not possible reimbursement will be made upon notification by card or letter of the amount due. THE CENTER CANNOT ACCEPT MATERIAL WHICH IS SENT COLLECT. Reimbursement cannot be made for packing or other charges beyond actual transportation. When possible, periodicals should be tied together by volume. It will be helpful if missing issues are noted on incomplete volumes.

K. R. SHAFFER,
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REPORT OF ADVISORY COMMITTEE ON GASTRO-ENTEROLOGY
OF THE
AMERICAN BOARD OF INTERNAL MEDICINE

Since the report of November, 1945, the Committee has conducted 2 examinations as follows:

At Chicago, February, 1946.

3 candidates were examined.

1 not passed by the Gastro-enterological Committee.

2 passed by the Gastro-enterological Committee and certified in Gastro-enterology, the names are as follows: Ludwig Frank, Charleston, West Virginia; Samuel A. Overstreet, Louisville, Kentucky.

At Philadelphia, May, 1946.

10 candidates were examined.

5 not passed by the Gastro-enterological Committee.

5 passed by the Gastro-enterological Committee and certified in Gastro-enterology, the names are as follows: Francis E. McDonough, 605 Commonwealth Avenue, Boston, Massachusetts; Hirsch R. Liebowitz, 177 New York Avenue, Brooklyn, New York; Tim J. Manson, 115 City Line, Bala, Pennsylvania; Emanuel M. Rappaport, 148-29 89th Road, Jamaica, New York; Victor W. Logan, 420 Bryn Mawr Avenue, Cynwyd, Pennsylvania.

Summary: of the 13 candidates examined by the Advisory Committee, 7, or 54% were passed, making 46% of failures.

The increased percentage of failures was apparently due to the fact that many of the candidates were returning service men who had not taken the time to orient themselves thoroughly in the requirements of our specialty.

The Advisory Committee on Gastro-enterology has acted on the principle that diplomates in this subspecialty must have qualifications making it perfectly safe to certify them as specialists and as consultants in gastro-enterology. By keeping the standards high, by showing no favoritism and by having at least 2 members of the Committee check on any doubtful candidates, the Committee hopes to continue to make certification of real significance. The following requirements have been agreed upon by the Committee.

1. Requirements for Admission to the Examinations in Gastro-Enterology.

A. Professional Standing

The candidates must have at least 2 letters from recognized internists or gastro-enterologists, which must attest to the candidate's professional qualifications and ethical standing, whether he is

specializing in gastro-enterology and if not entirely, giving an opinion as to approximately how much of his work is devoted to it.

B. Education

1. The candidate must submit proof of adequately supervised training in the recognized gastro-enterologic procedures, including gastric and hepato-biliary function tests, proctosigmoidoscopy and gastro-intestinal roentgenology (film interpretation).
2. The candidate must present evidence of fulfillment of one of the following requirements:
 - a. Formal graduate course in gastro-enterology, full time for at least 8 months in a recognized institution.
 - b. Residency or fellowship for at least 1 year in gastro-enterology under tutelage of a recognized specialist.
 - c. In the absence of a and b, attendance and an active participation in a ward service or in a gastro-intestinal clinic, recognized in standing, for at least 5 years.
3. If requirement a or b under the above heading has been met, only 3 years of c will be required.

C. Practice

At least 60% of the candidate's work must have been devoted to gastro-enterology for at least 3 years before application.

2. Requirements for Certification in Gastro-Enterology.

After a candidate has successfully passed his examinations in Internal Medicine and is therefore a certified internist, he is examined by a team of gastro-enterological examiners, one of whom at least should be a member of the Advisory Committee on Gastro-Enterology. No candidate shall be rejected as a result of examination by only one examiner. In doubtful cases the candidate should be turned over to another team if possible.

Each candidate is assigned to a patient whose history and physical examination he reports to the examining team, and he is encouraged to ask for and to interpret any or other findings. He is then thoroughly quizzed by the team, not only in regard to the case presented, but in all subjects pertaining to gastro-enterology, including the basic science subjects having a bearing on gastro-enterology, the method and the interpretation of physical, laboratory, endoscopic and roentgenological examinations, the practical application of this knowledge to the management of given types of patients and the ethical aspects of hospital and consultant practice in a specialty.

The examiners should bear in mind that the candidate is to be certified as a specialist, a consultant, as one qualified to act as a gastro-enterologist

in any hospital or in the government service. While catch questions are to be avoided, the way the candidate handles questions the answers to which he does not know should influence the examiner's judgment of his fitness.

We are pleased to inform the Association that last December, Dr. Victor Johnson, Secretary of Council on Medical Education and Hospitals, promised that the Council will hereafter inspect and rate all residencies, fellowships, internships and post-graduate courses in gastro-enterology in the U. S. A.

Members of your Advisory Committee will serve with members of the Council on Committees assigned to inspect these facilities. This will finally put our specialty on a firm basis.

Respectfully submitted,
/s/ A. R. Andresen, Chairman

N.B. For further information regarding certification in Internal Medicine and in Gastro-enterology and for application blanks for the examinations, anyone interested should write directly to Dr. William A. Werrell, Asst. Secretary-Treasurer, American Board of Internal Medicine, 1 West Main Street, Madison, Wisconsin.

BOOK REVIEWS

GASTROENTEROLOGY (In three Volumes). Volume III. By *Henry L. Bockus, M.D.* W. D. Saunders Company, Philadelphia and London, 1946. 1091 pp. Price 3 volumes, \$35.00.

The third volume of Bockus' Gastroenterology deals with diseases of the liver, the biliary tract, the pancreas and some secondary gastrointestinal disorders. Many of the chapters are written by associates of Dr. Bockus on the faculty of the University of Pennsylvania Graduate School of Medicine.

As in the case of the first two volumes, the chapters are well written and crammed with up-to-date information. There are good and useful bibliographies. There is such a wealth of material that it is hard to know what to comment on. The reviewer is particularly pleased to find the statement that "the gallbladder that is supposed to empty slowly is really re-filling because of re-absorption of dye from the bowel." It is most gratifying to find the statement that a "gallbladder must never be operated on because it empties slowly." The writer might have added that it will be a great day for gastroenterology when radiologists stop commenting on slowly emptying gall-bladders and thus remove temptation from the pathway of surgeons.

It is good to find a chapter on the functional disorders of the gastrointestinal tract of neuropsychiatric origin. One's only regret is that it is so short. This tremendously important subject gets only 29 pages. The subject of visceroptosis, which might have been dismissed with a sentence, gets nineteen pages.

The chapter on animal parasites by Rothman is very interesting and well illustrated. It is good to find a chapter on gastrointestinal allergy. There are other chapters on the inter-relationship between cardiac and gastrointestinal disorders, on the digestive symptoms of pulmonary tuberculosis, and on the digestive disturbances that are secondary to disease in the genito-urinary organs.

Again the reviewer wishes to congratulate Dr. Bockus on a tremendous job, wonderfully well done. No gastroenterologist can well afford to be without these three fine volumes. A careful reading of them would supply a good graduate course in gastroenterology.

MEDICAL DIAGNOSIS. Edited by *Roscoe L. Pullen, M.D.* W. B. Saunders Company, Philadelphia and London, 1945. 1106 pp. Price \$10.00.

Dr. Pullen has produced a most attractive book and a very useful one on medical diagnosis. In these days of great specialization, he has been wise to get a large group of specialists to help him with the several chapters. The book is unusual in that there are chapters on special examinations. For instance, there is a chapter on the neurologic examination and others on the endocrine survey, the endocrine survey of sexual and reproductive systems, the psychiatric approach, the differential diagnosis of neurosis and psychosis, practical mental measurement, clinical electroencephalography, the differential diagnosis of the causes of coma, pediatric physical diagnosis, the sterility survey, occupational injury, military problems, and determinates of prog-

nosis. In addition, there are chapters on the examination of the different parts of the body. There are good chapters on the gynecologic and obstetric diagnosis, on urologic diagnosis, and anorectal diagnosis.

It is always a pleasure to find a book which has been organized along new and modern lines. Too often the writers of textbooks stick to the old chapter headings that were used at the beginning of the century or earlier. The book is well written and well illustrated, and there are short bibliographies appended to some of the chapters. Particularly interesting is Dr. Harry Dingman's chapter on "Determinates of Prognosis." As medical head of a large insurance company, Dr. Dingman knows whereof he speaks.

It was a wonderful idea also to put in the chapter by Dr. Merrill Moore on "The Psychiatric Approach." As Dr. Moore says, "The psychiatrist should bring to his patient's problem an understanding heart. The understanding heart is the same thing in psychiatry that the 'green thumb' is in gardening." As Dr. Moore goes on to say, it would be well if at some time the psychiatrist had some nervous difficulty of his own that could sensitize him to the suffering of others and give him understanding and sympathy. As Dr. Moore says also, the psychiatrist must be a person of distinction and strength so that he can be a leader. He must be a bit of a philosopher. Dr. Moore's approach to his problems is very sane, and he is concerned with that type of patient who comes to the clinician and the average physician.

This is a book which every physician would do well to have on the bookshelf near his bed for a little reading before he goes to sleep at night.

THE PERSON IN THE BODY. An introduction to Psychosomatic Medicine. By Leland E. Hinsie, M.D. W. W. Norton & Co., Inc., New York. 263 pp. \$2.75.

This little book, written by an eminent professor of psychiatry, apparently for laymen, leaves the reviewer a bit disappointed because it is not quite what he would expect either as an introduction to psychosomatic medicine or as a book for the instruction of the lay reader. It sounds a bit technical for the layman, and one questions the wisdom of putting in lay hands some of the material in the book. The ordinary physician reading it will probably wish there were less about Freudian ideas and more about the type of nervous, worrisome and neurotic person he sees every day in his office.

Dr. Hinsie appears to have written a good book for graduate students in psychiatry, but he hasn't quite overcome the great difficulties of writing on a technical subject in non-technical language. That is a rare gift of the gods, and one that is terribly needed today.



Clement R. Jones

Clement R. Jones 1871-1945

On September 3rd, 1945, Doctor Clement Russell Jones died at the age of seventy-three, of a Coronary Occlusion, at his home in Pittsburgh, Pennsylvania. With his passing our Society loses a past-president noted for his thoughtfulness, courtesy, geniality, kindliness, loyalty to his chosen profession, and his contributions to therapeutics. Doctor Jones was a graduate of Ohio State University, Class of 1892, and was the last surviving member of the original staff of Presbyterian Hospital, serving there since its founding in 1894. He practiced medicine in Pittsburgh for over fifty years.

Doctor Jones served as Treasurer of the American Gastro-Enterological Association from 1919 to 1929. He was elected second vice-president in 1930, and in 1931 succeeded to the presidency of our Society. His contributions to the literature in his chosen field of gastroenterology were many and varied. Of special note is a paper he presented in 1921 at the annual meeting of our Society on "Hematemesis." In this presentation Dr. Jones called attention to the allaying of a patient's fears as being the most difficult part of the treatment, and also suggested frequent feeding of a gelatin mixture. He was one of the first American clinicians to advocate immediate feeding in the treatment of bleeding peptic ulcer.

Doctor Clement Jones was one of the Founders of the American College of physicians, and was instrumental in influencing outstanding clinicians to affiliate with the college. In the early days, he advocated the establishment of its headquarters near the geographical center of the United States. He was a regent and the second treasurer of the college. From a small bank account, when he took office, he saw the Association grow into substantial proportions, and he alone was responsible for the investment of the funds in suitable securities.

Doctor Jones was a past president of the American Therapeutical Society. An active member of the faculty of the school of dentistry of the University of Pittsburgh since 1896. He occupied the chair of *materia medica* and *therapeutics and principles of medicine* at the time of his death. In 1934 he was appointed as an instructor at the school of medicine, University of Pittsburgh, and from 1938 until the time of his death he was associate professor of medicine.

During World War I Doctor Jones served as chairman of the Red Cross Disaster Committee, and functioned actively in this capacity during the 1918 influenza epidemic.

He was a member of the senior staff of Mercy Hospital in Pittsburgh, and on the staffs of the Presbyterian Hospital, the Falk Clinic (University of Pitts-

burgh, School of Medicine) and Pittsburgh City Home and Hospitals (Mayview).

He is survived by his wife, Margaret Elson Jones, and three sons, Doctor Clement R. Jones, Christy Jones, and Dr. Elson Jones.

Not alone has he left an impression on his immediate locality, where he devoted himself to the practice of medicine, but nationally the medical profession as a whole has benefitted by his broad concepts, as exemplified in the American College of Physicians, and his efforts in behalf of the special branch of Medicine—Gastroenterology—to which he devoted the greater part of his time.

A. A. AARON.

Alexander Berkeley Moore

Alexander Berkeley Moore, M.D., F.A.C.P., was born at Aldie, Virginia, on November 8, 1883. He graduated in Medicine from the University of Virginia, after which he served as interne at the University of Virginia Hospital. For two years he practiced medicine at The Plains, Virginia, after which he entered the Mayo Clinic as Associate in Roentgenology.

When this country entered the First World War, Dr. Moore enlisted in the Medical Corps and served from August 1917 to March 1919. He then returned to the Mayo Clinic and in 1926 was appointed Chief of the Section of Roentgenology. He was also made Associate Professor of Roentgenology of the Mayo Foundation. He wrote and published at least thirty original essays of great merit.

In 1930 he was offered a teaching position in the George Washington University Medical School. This he accepted and he came to Washington, D. C., where he was not only associated with George Washington University but became one of the firm of Drs. Groover, Christie & Merritt, who are the leading roentgenologists of this city. He was chief in Roentgenology at the Emergency Hospital until his death on March 8, 1946.

Dr. Moore was a member of the American Gastroenterological Society for some twenty years. He had an unusual talent for friendship and was greatly beloved by those who knew him. This is exemplified by a certificate he received when he left The Mayo Clinic, signed by all the staff. This certificate reads, "To live honorably among men, to work skillfully for their good, to hold steadfastly their friendship, are evidences of high character. Inasmuch as these qualities are exemplified in Alexander Berkeley Moore, for many years our good colleague, we bestow upon him this token of our esteem."

WILLIAM EARL CLARK.



Alexander Berkeley Moore

ABSTRACTS OF CURRENT LITERATURE

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MOUTH AND ESOPHAGUS

ABOWITZ, J. Diaphragmatic hernia and dilated esophageal ampulla—their clinical and diagnostic significance. Am. J. Roent. Rad. Therapy, 54: 483 (Nov.) 1945.

Acquired diaphragmatic hernia and dilatation of the esophageal ampulla are relatively common. Two types of diaphragmatic hernia are noted: (1) para-esophageal with hernia of the stomach displacing the esophagus laterally, and (2) the stomach and the esophagus protrude together into the mediastinum. The author also discusses a pseudo-hernia—an enlarged esophageal ampulla due to spasm.

The dilated esophageal ampulla may or may not produce symptoms. There may be dyspnea, prostration, bloating, and pressure in the precordial region—aggravated by a heavy meal or when the patient is in a recumbent position. In the presence of aerophagia the symptoms are aggravated even in the erect posture. This condition may also produce reflex symptom which may stimulate gall bladder or heart disease.

MAURICE FELDMAN.

BOWEL

WILSON, A. K. Roentgen examination in congenital intestinal obstructive defects in infants. Am. J. Roent. Rad. Therapy, 54: 498 (Nov.) 1945.

In 9,474 living babies, the author found 2 cases of obstructive congenital intestinal anomalies (imperforate anus and atresia). A description of the embryological formation of obstructive defects is given. The X-ray method of diagnosis, recommended by Wangensteen and Rice, is described. This method consists of placing an opaque object in the anal dimple. With the baby suspended head down, the gas rises to the highest point in the lower bowel. The extent of separation between the blind end of the rectum and the perineum is demonstrated. Wilson described 2 cases of imperforate anus and one case of an enterocyst in the left upper quadrant. In the later case, the contrast medium given as an enema revealed the cystic mass.

MAURICE FELDMAN.

- LYALL, A. Treatment of acute appendicitis—a study of 480 consecutive cases. *Brit. Med. J.*, 4429: 719 (Nov.) 1945.
The author reported 480 cases of acute appendicitis, classifying them into 4 groups:
(1) Acute or catarrhal appendicitis without peritonitis; 177 cases, appendectomized without mortality.
(2) Acute appendicitis with local peritonitis; 188 cases, all but 2 of which were appendectomized. All but 2 were closed without drainage. In those with sero-purulent fluid, irrigation of the tissues with acriflavine solution and dusting with sulphanilamide powder were carried out. In this group there was no mortality.
(3) Acute appendicitis with spreading peritonitis; 52 cases. The appendix was ruptured in all but 4. Twenty-seven of this group were classified as desperately ill. Only 1 case was treated by the delayed method. Sulphanilamide was used freely in this group. All but 4 of the cases were drained. The mortality rate was nil.
(4) Appendiceal abscess; 63 cases, 3 of which were treated by the delayed method. In all but 4 instances the appendix was removed at the time of the operation. The only 2 deaths of the entire series of 480 cases occurred in this group.

The author discussed the various special points in treatment, such as the anesthetic, fluid and chloride replacement, time of operation, abdominal incision, use of sulphonamides, and drainage. An evaluation of the factors responsible for the morbidity and fatality rates was given. The important factors were the prompt use of intravenous therapy to restore fluid balance and the intraperitoneal use of sulphanilamide powder.

MAURICE FELDMAN.

- FITZGERALD, P. J., AND KINNEY, T. D. Intestinal lipodystrophy (Whipple's disease). *Am. J. Path.*, 21: 1096 (Nov.) 1945.

The authors report the eighth case of intestinal lipodystrophy to be recognized since Whipple first described the disease in

1907. Clinically, the disease is usually characterized by asthenia, anemia, abdominal distress, and steatorrhoea. The anemia is usually of a hypochromic type, but in the present case the blood picture was bizarre in that lymphatic leukemia and hemolytic icterus were seriously considered. At autopsy, the mucosa of the entire jejunum and ileum was found filled with a white fatty substance which could be expressed from a cut surface. The lesion ended abruptly at the ileocecal valve. The mesenteric nodes averaged 2 cm. in diameter and the cut surface was pale gray with pin-head sized discrete nodules scattered throughout. The liver was enlarged and there was focal necrosis of the adrenal glands. Analysis of the intestinal wall in terms of mg. per 100 mg. of dried tissue gave total cholesterol 3.16, total phospholipids 14.95, and total fatty acids 19.9.

The cause of the disease is unknown. The pathological changes seem limited to the structures concerned with fat absorption and there is no involvement of other lymphatic tissue in the body. Temporary improvement from the administration of bile salts occurred in one patient.

N. W. JONES.

- HATFIELD, C. A., BUYERS, R. A., AND WALKLING, A. A. Fluorescein—its use in determining the viability of strangulated intestine. *Surg. Gyn. Obs.*, 81: 530 (Nov.) 1945.

The use of fluorescein is a relatively new diagnostic aid that appears to be accurate and simple. A form of resorcinophthalein, fluorescein is extremely diffusible, and it absorbs ultraviolet rays of long wave lengths. When these rays of 3,660 Angstrom units strike fluorescein, they are instantly converted into the longer light waves of the visible spectrum.

Five cases are reported in which fluorescein was injected intravenously and an ultraviolet lamp with a Wood's filter was used to determine fluorescence in damaged bowel. The presence of fluorescence was sufficient evidence of viability to permit return of these damaged loops of bowel to the abdominal cavity. The absence of fluo-

rescence was diagnostic of nonviability confirmed by microscopic section.

Postoperative course and pathological sections seem to bear out the prognosis based on the fluorescein method. Evidence seems adequate that this relatively simple method removes the uncertainty from a diagnosis which never had been classified as exact.

FRANCIS D. MURPHY.

HODES, P. J., AND KEEFER, G. P. Hookworm disease—a small intestinal study. Am. J. Roent. Rad. Therapy, 54: 728 (Dec.) 1945.

Most of the pathology occurring in hookworm disease is found in the small intestine. Grossly, the small intestine shows small punctate hemorrhages where the mouths of the worms are embedded. These may form erosions or ulcerations.

About 60% of the patients observed had clinical evidence of hookworm disease. Itching was the first sign noted, and it was localized to the exposed skin. Cough was a common manifestation, appearing 1 to 2 weeks after the itch. Examination of the lungs showed no Roentgen abnormalities. The time of onset of gastrointestinal symptoms varied from 6 to 25 weeks after exposure. In many there was an acute attack of nausea, vomiting, abdominal pain, diarrhea, and occasional low grade fever. The blood examination revealed a leukocytosis and eosinophilia.

In 60% of the patients the hookworm infestation revealed gastrointestinal abnormalities. The esophagus and stomach were negative. Gastric emptying was usually normal, as was the duodenal bulb. In the third and fourth portions of the duodenum there was increased tone manifested by narrowing of the lumen and irritability. There were also mucosal distortions with thickening of the folds. The distal duodenum showed a transient dilatation. The latter change was more often noted in the jejunum. Jejunal tenderness was the earliest manifestation of hookworm disease.

Narrowing of the intestinal lumen and mucosal distortion characterized the Roentgen findings. Both segmental and peristaltic contractions were increased. There

were active pendular movements which had an accordion-like or cog-wheel appearance. The peristalsis was vigorous and rapid. In the jejunum the mucosal folds were 2 or 3 times as wide, and were spaced irregularly. The folds appear thick and irregular. There was an uneven increase in the height and irregular manner in which they dipped into the column of the barium. The ileum usually revealed nothing abnormal. The changes are considered to be due to an abnormal intramural nervous system.

MAURICE FELDMAN.

TAN, C. C., and LIU, Y. Amebic colitis with special reference to perforation—a study of 20 autopsied cases. Chinese Med. J., 62: 366 (Oct.-Dec.) 1944.

Among 349 clinically diagnosed cases of amebic colitis, observed between 1920 and 1940, there were 11 with intestinal perforations. Two perforations of the cecum were excluded on account of a concomitant bacillary infection. The largest number of cases were observed in the fourth decade of life. In contrast to the common occurrence of bacillary infections in children, amebic infections are seen more frequently among the middle aged. Most patients belonged to the poorer classes. The disease was most frequent during July and August. The onset was sudden in all cases, and in 3 instances it was fulminating. Frequent bloody and mucopurulent stools, abdominal pain, and tenesmus were the common symptoms. Fever and chilliness occurred in cases complicated by liver abscess, peritonitis, or pneumonia. All showed slight anemia and leucocytosis. Diagnosis of perforation frequently was difficult. Patients usually were admitted in a critical condition, weak, emaciated, and exhausted. Abdominal findings often were so indefinite that in the early stage the signs of peritonitis were overlooked. In 6 of the 9 cases of perforation the diagnosis was, however, made before death occurred.

The common early findings of perforation are abdominal distension, tenderness, and muscle spasm. Emetine is not effective in controlling perforation after the anatomical lesions reach an advanced stage. Once perforation occurs, the chance of recovery is

slight. One patient survived perforation of the cecum and the formation of a fecal fistula. More than half of the cases showed varying degrees of diffuse ulceration. The sigmoid colon and the cecum were more frequently involved than elsewhere, but the cecum had the severest lesions and largest number of perforations. The ileum was involved in 7 out of 20, and the appendix in 5 out of 15 cases examined. The cecum was perforated in 5 instances, the descending colon in 4, the sigmoid in 2, and the transverse colon in 1. Multiple perforations were found in 2 cases.

H. NECHELES.

STALKER, L. K. Intra-abdominal hernia with acute intestinal obstruction. N. Y. State J. Med., 45: 2307 (Nov.) 1945.

This is a rather rare condition, most cases developing secondarily to some operative procedure. A case of herniation of a loop of ileum through the left broad ligament, with subsequent intestinal obstruction, is reported, and the mechanism of its production is discussed.

PHILIP LEVITSKY.

BROWN, S. Chronic nonspecific regional enteritis. Am. J. Roent. Rad. Therapy, 54: 487 (Nov.) 1945.

All observers have revealed an increase in the frequency of chronic non-specific enteritis. Although the pathologic process usually involves the terminal ileum, no part of the small or large intestines is exempt. A brief discussion of the pathologic process and etiology is given. There are no pathognomonic signs or symptom-complex, though there are symptoms strongly suggestive of intestinal disturbance, namely, abdominal pain and tenderness usually limited to the right lower quadrant, diarrhea with stools containing mucus and sometimes blood, and occasionally a palpable mass. Emphasis is placed upon the Roentgen examination, which has proved to be the most useful method for diagnosis. The following Roentgen signs are given in the order of importance and frequency: (1) deformity of contour of the bowel wall, (2) narrowing of the lumen, (3) loss of mucosal pattern, (4) constrictions of the bowel, (5) rigidity of the in-

volved segment, (6) displacement of adjoining segments of bowel due to pressure by pseudo-tumors, (7) internal fistula, (8) hypermobility of intestinal contents, and (9) stenosis with dilatation of proximal bowel. Twelve cases are described with Roentgen illustrations.

MAURICE FELDMAN.

DARBY, W. J., AND JONES, E. Treatment of sprue with synthetic *L. casei* factor (folic acid, vitamin M). Proc. Soc. Exp. Biol. Med., 60: 259 (Nov.) 1945.

The similarities of the sprue syndrome in man to the manifestations of vitamin M (*L. casei* factor, folic acid) deficiency in the monkey are obvious. *L. casei* factor is curative for vitamin M deficiency in monkeys. *L. casei* factor was used in the treatment of 2 cases of non-tropical sprue. The daily intramuscular injection of 15 mg. of the synthetic material was used as the sole therapeutic agent. Under this treatment, glossitis disappeared, reticulocytosis and increase in thrombocytes occurred, diarrhea disappeared, weight was gained, and the glucose tolerance curve became more normal.

These preliminary results demonstrate that the two cases of sprue have improved markedly. It is reasonable to attribute the improvement to a specific effect of the substance administered, although the possibility of spontaneous remissions in these patients cannot be ruled out.

H. NECHELES.

SMYTH, C. J., BRUNDAGE, R., ORTEN, J. M., AND SMITH, A. H. Fumaric acid salts as hydrogogue cathartics. Proc. Soc. Exp. Biol. Med., 60: 301 (Nov.) 1945.

The 4 preparations studied—magnesium fumarate, calcium fumarate, sodium fumarate, and Rochelle salts—were administered by dissolving the salt in half a glass of water, using either 10 g. or 15 g. doses. Each salt was given to relieve 2 successive periods of constipation. Each patient received in succession all 4 salts or as many as the period of hospitalization, or the extent of the constipation, or both would permit. The sequence of administration of the salts was not constant.

Of a total of 143 patients studied, 111 pa-

tients received doses of 10 g. each, 5 patients were given 15 g. per dose, and 27 patients first were given doses of 10 g. and later doses of 15 g. each. When the laxative actions of sodium, magnesium, and calcium fumarates were compared with that of sodium potassium tartrate in 143 chronically constipated patients, the fumarates were found as satisfactory as Rochelle Salts.

H. NECHELES.

LIVER AND GALL-BLADDER

RECANI, L., CHARGAFF, E., AND HANGAR, F. M. Comparison of the cephalin-cholesterol flocculation with the thymol turbidity test. *Proc. Soc. Exp. Biol. Med.*, 60: 245 (Nov.) 1945.

The thymol turbidity test was described in 1944 by MacLagan. There is a marked parallelism between the thymol test and the cephalin flocculation test, both which depend upon alterations of the serum in certain liver diseases. The thymol test is performed by adding 0.05 cc. of the serum to 3 cc. of saturated thymol in barbiturate buffer. The intensity of the turbidity within 10 minutes indicates the degree of active liver damage.

The authors confirmed the findings of MacLagan that the test is usually positive in cirrhosis, hepatitis, etc., in which the cephalin flocculation is also positive. Notable exceptions were as follows: The thymol test was positive and the flocculation negative in (1) lipemic sera, such as occur in diabetes and in nephrosis; (2) biliary cirrhosis; (3) certain cases of metastatic neoplasm of the liver; (4) convalescent hepatitis; and (5) certain normal sera. The thymol test was negative and the flocculation test positive in normal laboratory animals such as dogs and rabbits, and in certain rare cases of presumably normal individuals with no demonstrable liver disease.

Differences in the mechanisms of the cephalin flocculation and the thymol test are as follows: The gamma globulin fraction upon which the cephalin flocculation depends, is not an essential factor in the thymol test. The electrophoretically derived albumin fraction has no effect on the intensity of the thymol test. On the other hand, the albumin fraction is an important factor in

the flocculation reaction, since normal albumin inhibits flocculation, while that derived from hepatitis serum fails to inhibit. The presence of lipids is necessary for a positive thymol test, but has little effect on the cephalin flocculation reaction. There is no evidence that an abnormal lipid is present in hepatitis serum, since the negative thymol test obtained after ether extraction can be made positive once more by a variety of lipid preparations and even by whole normal serum. Lipids alone give no reaction with thymol. It must be assumed that an abnormal constituent in the serum in addition to lipids is required for a positive thymol test. If the standard thymol solution is prepared with physiological salt solution instead of distilled water, all tests become negative. In contrast, the cephalin flocculation is routinely performed in salt solution which has no effect on the flocculation or precipitation.

H. NECHELES.

WATSON, C. J., AND RAPPAPORT, E. M. A comparison of the results obtained with the Hangar cephalin-cholesterol flocculation test and the MacLagan thymol turbidity test in patients with liver disease. *J. Lab. Clin. Med.*, 30: 983 (Dec.) 1945.

The Hangar cephalin-cholesterol flocculation test and the MacLagan thymol turbidity test were carried out for comparative purposes on 145 individuals. Thirty-one of these were normal, 60 were suffering with hepatitis, 13 with cirrhosis and subacute atrophy, 12 with extra-hepatic biliary obstruction, 4 with hepatic carcinoma, 1 with inoculation malaria, and 18 with miscellaneous conditions. Two hundred and fifty-two tests were performed, and agreement was noted in 225 (89%). In the MacLagan test, 4 units was accepted as the upper limit of negativity, and for the Hangar test, the limit was a trace for 24 hours, or 1 plus for 48 hours. The majority of cases of disagreement, especially in the hepatitis group, were borderline. More serious discrepancies were seen in 2 cases of subacute atrophy, 1 case of cirrhosis, and in 6 cases of proved cancer. Even in the 225 cases of agreement, there was no quantitative correlation in many instances. The authors con-

clude that the underlying basis of the two tests is different. It appears that the MacLagen test is more often negative in patients with serious liver disease. It has the advantage over the Hangar test of relative simplicity and rapidity, and it can be used as a routine procedure and in following the progress of a disease, once the diagnosis has been established. A strongly positive value by the MacLagen test is just as indicative of liver disease as by the Hangar test.

PHILIP LEVITSKY.

BOYD, E. M., PERRY, W. F., AND STEWART, W. C. The choleretic action of dehydrocholic acid (Decholin) and deoxycholic acid (Degalol) in chronic biliary fistula dogs. *J. Pharm. Exp. Therap.*, 85: 343 (Dec.) 1945.

Decholin and Degalol were given *per ora* in a dose of 0.1 gm. kg. body weight to 16 unanesthetized chronic biliary fistula dogs. Over a period of 3 days, both drugs produced an increased volume output of hepatic bile, but no significant change in its specific gravity, relative viscosity, total solids, sodium, potassium, chlorides, inorganic phosphate, total fatty acids, total cholesterol, ester cholesterol, free cholesterol, bilirubin, or bile acid contents.

ARTHUR E. MEYER.

BRUNSWIG, A., JOHNSON, C., AND NICHOLS, S. Carbon tetrachloride injury of the liver. The protective action of certain compounds. *Proc. Soc. Exp. Biol. Med.*, 60: 388 (Dec.) 1945.

Previous work on dogs showed that sodium thioglycocholate protected the liver against acute chloroform injury, as did protein and methionine. This was interpreted as showing the importance of the -SH group in the protective mechanism. This report is a study of the protective action of certain -SH and other compounds against acute hepatic injury by carbon tetrachloride in the rat. Histologic criteria were employed. Injection of 0.1 cc. of carbon tetrachloride subcutaneously into rats weighing 150 g. results in characteristic hepatic lesions in 24 hours. The various agents were injected intraperitoneally immediately following the injection of carbon tetrachloride. Twenty-four hours

later the livers were removed for histologic study. Since an occasional animal appears to be resistant to the effects of carbon tetrachloride, a definite protective action was ascribed to an injected agent only if at least 40% of the animals showed deviations from the controls. A very marked protection was afforded by sodium thioglycocholate; considerable protection was obtained with sodium glycocholate. Glutathione afforded appreciable protection. Sodium thiomate, sodium malate, and cysteine afforded definite protection but less marked. Aspartic acid, glutamic acid (both as sodium salt), sodium acetate, methionine, choline alone, and choline plus cystine did not afford significant protection.

A protective action against injury by carbon tetrachloride does not necessarily depend upon the presence of -SH, as previously reported concerning the protective action of protein and other agents against chloroform injury of the liver in dogs. The disturbances in the liver by chloroform and carbon tetrachloride probably represent different phenomena and vary in different animals. Methionine afforded protection against chloroform injury in dogs, but did not afford protection against carbon tetrachloride injury in rats.

H. NECHELES.

ROBERTSON, H. E., AND FERGUSON, W. J. The diverticula (Luschka's crypts) of the gallbladder. *Arch. Path.*, 40: 312 (Nov.-Dec.) 1945.

The authors discuss in detail their conception of the significance of the peculiar outpouchings of the mucosa of the gallbladder known as Luschka's crypts or Rokitansky-Aschoff sinuses. This is based on their study of 495 gallbladders removed at operation or at autopsy, as well as the literature. They conclude that the mucosa is found invaginated into the underlying structures in more than $\frac{1}{3}$ of the gallbladders removed from persons over 30 years of age. These invaginations tend to form diverticula, with branching pouches which may resemble mucous glands. They are lined with epithelium similar to that of the gallbladder. Some of them open into the lumen of the gallbladder by means of ducts. Some are

cut off and form cysts. They are not adenomata, but rather "multilocular cystic diverticula." The crypts thus formed may contain bile, bile pigments, crystals, or calculi. They may be the seat of exudative inflammation or abscess formation, and may even rupture into the peritoneal cavity. The authors believe that increased intracystic pressure, the absence of muscularis mucosae, and the loosely arranged muscular layer about the diverticula with independent response of the muscle bundles to physiologic stimuli, account for the initial diverticulum-like indentations.

N. W. JONES.

POLLOCK, M. R. Liver function in infective hepatitis gauged by hippuric acid synthesis tests. *Brit. Med. J.*, 4433: 878 (Dec.) 1945.

The hippuric acid test was utilized to follow the course of liver damage in 81 cases of infected hepatitis. This test is probably the most reliable guide to liver function in the presence of jaundice. Serum bilirubin and hippuric acid tests were carried out in each case. A summary of the results shows that (1) the hippuric acid synthesis reflects the severity of the attack and the stage of the disease, rather than a direct correlation with the serum bilirubin concentration; (2) there is a considerable increase in the hippuric acid values during the first 6 days.

There is a progressive improvement in liver function as judged by the hippuric acid test, although initially in half of the cases the serum bilirubin concentration and jaundice were actually increasing. It is possible that the apparent disassociation of these two functions might be explained by the fact that bilirubin is formed in the body at an approximately constant rate and that the efficiency of the liver be judged by the amount of bilirubin excreted each day, rather than the concentration of the serum. As far as the bilirubin is concerned, liver function should be gauged by the rate of rise or fall of the serum concentration. It is shown that the maximum liver damage occurred before admission in most cases.

MAURICE FELDMAN.

LOWRY, J. V., ASHBURN, L. L., AND SEBRELL, W. H., JR. Treatment of experimental

liver cirrhosis. *Quart. J. Studies Alcohol*, 6: 271 (Dec.) 1945.

Rats were maintained on a cirrhosis-producing diet for 63 to 84 days, and the status of the liver of each rat was determined at that time by means of a biopsy. The rats were then treated by the daily administration of large amounts of choline chloride or by using a diet containing larger amounts of casein. The gross and histological appearance of the liver after treatment was compared with the biopsy findings. During the period of treatment, a striking improvement in the gross and microscopic appearance of the liver occurred. Although therapy had no recognizable effect on the fibrous tissue present, it apparently prevented further progression of the cirrhotic process and produced a marked improvement in the histological appearance of the parenchyma.

ALBERT CORNELL.

PANCREAS

RIENHOFF, W. F., JR. AND PICKRELL, K. L. Pancreatitis—an anatomic study of the pancreatic and extrahepatic biliary systems. *Arch. Surg.*, 51: 205 (Nov.-Dec.) 1945.

Possible etiological factors of pancreatitis are as follows: (1) A calculus may block the duodenal orifice of the ampulla, so that the common bile and pancreatic ducts form a communicating system, allowing bile to flow up the pancreatic duct and infiltrate the pancreas. (2) The sphincter at the duodenal end may become spastic and produce the same condition. (3) The pancreas may be infected by bacteria which reach it by way of the lymph channels from a diseased gallbladder, or from a focus of infection by way of the blood stream. (4) Any obstruction of the pancreatic duct complete enough to cause sufficient back pressure of the pancreatic secretions may result in dilatation of the ducts and rupture of the acini, releasing the pancreatic ferments with resulting hemorrhage, fat necrosis, etc.

The anomalies and their results encountered in 250 dissections of the pancreatic system are tabulated and discussed. In 73 instances, no junction of the pancreatic and bile ducts was found, each entering the duodenum with separate orifices. In 92, the ducts were contiguous, but in this group

no true ampulla was present. In 81, a true ampulla was present, and in 4, the main pancreatic duct was reduced to a fibrous cord. In 47, the length of the ampulla exceeded the average diameter of the duodenal orifice; a complete block at the papilla would convert the 2 ducts into a communicating system. Concerning the accessory pancreatic duct, in only 89 of 100 specimens studied could any intraglandular communication between the ducts be demonstrated.

FRANCIS D. MURPHY.

ANEMIAS

SPIES, T. D., VILTER, C. F., KOCH, M. B., AND CALDWELL, M. H. Observations of the anti-anemic properties of synthetic folic acid. *Southern Med. J.*, 38: 707 (Nov.) 1945.

The high incidence of macrocytic anemia found among patients in the Nutrition Clinic, Birmingham, Alabama, has not only stimulated a study of the natural history, morphology, and etiology of the disease, but has also offered opportunity for the study of reticulocytosis and erythropoiesis. Numerous substances have been tested and the effects noted on the clinical progress of the patient, on reticulocytosis, leukocytic equilibrium, and red cell and hemoglobin regeneration. The reticulocytosis which occurs following the administration of a synthetic substance, *Lactobacillus casei* factor, which is considered a part of the B complex, is of such interest as to warrant this report. The synthesis of the *L. casei* factor has been announced by sixteen investigators at the Lederle Laboratories and the Calco Division of the American Cyanamid Company. The Lederle Laboratories supplied the material for clinical trial; it is described as active for *L. casei* and *S. Faecalis R*, and as promoting growth and hemoglobin formation in the chick.

L. casei factor, dissolved in saline made alkaline with small amounts of sodium bicarbonate, was given intravenously to 5 subjects with macrocytic anemia in relapse. All of the patients were admitted to the hospital during a control period and during therapy. The diet was rigidly controlled, with elimination of meats and meat products. It is obvious from the results described that persons with macrocytic anemia

in relapse have a significant hemopoietic response following the administration of synthetic folic acid. This response follows either parenteral injection or oral administration; of course, cases will be found that do not absorb satisfactorily from the alimentary tract, and they will not respond. In every instance the number of reticulocytes increased in the peripheral blood, and the red blood cell counts and hemoglobin content rose toward normal levels.

IRVING GRAY.

LANGE, R. D., RAMSEY, R. H., AND MOORE, C. V. The urinary excretion of antipericious anemia factor. *J. Lab. Clin. Med.*, 30: 1048 (Dec.) 1945.

The extract was prepared by evaporating the urine to dryness under reduced pressure. Ethyl alcohol was added and the mixture filtered. The filtrate was then evaporated and the residue taken up in sterile water. The 24-hour urine specimen of a healthy male adult who had been given liver extract parenterally was thus treated. Another extract was prepared from a pernicious anemia patient in relapse and under active treatment. Neither of these preparations gave a reticulocyte response, after injection in a human. The experiment was controlled by first adding liver extract to the urine, and then subjecting the whole to extraction by the above method. The material thus obtained gave a satisfactory reticulocyte response. The report concludes that according to the method of extraction used, no A.P.A. factor is excreted in the urine of individuals receiving liver extract.

PHILIP LEVITSKY.

MOORE, C. V., BIERBAUM, O. S., WELCH, A. D. AND WRIGHT, L. D. The activity of synthetic *Lactobacillus casei* factor ("folic acid") as an antipernicious anemia substance. I. Observations on four patients: Two with Addisonian pernicious anemia, one with nontropical sprue and one with pernicious anemia of pregnancy. *J. Lab. Clin. Med.*, 30: 1056 (Dec.) 1945.

Synthetic *L. casei* factor (folic acid) was given orally to two patients with pernicious anemia. Meat was withheld from the diet. The reticulocyte response and the clinical

improvement were comparable to that seen following liver therapy. Similar improvement was noted with the synthetic *L. casei* factor was administered intravenously to 1 patient with non-tropical sprue, and to one woman with pernicious anemia of pregnancy. Two normal individuals were used as controls. One was given the factor by mouth, and the other received it intravenously. There were no untoward reactions and no changes in the blood picture. The authors feel that the synthetic *L. casei* factor has antipernicious anemia properties rather than extrinsic factor activity. This antipernicious anemia factor may not be identical with that found in liver.

PHILIP LEVITSKY.

ULCER

DRIVER, R. L. Effects of temperature on the experimental production of ulcers in the intestines of dogs. Am. J. Dig. Dis., 12: 394 (Dec.) 1945.

This investigator previously determined the activity of an enzyme as a function of temperature. A study of the temperature effect was made on isolated loops of intestine of dogs by introducing solutions through a "T" cannula at predetermined temperatures of 5, 25, 40 and 45 degrees C. The digestive action of a 0.1 per cent pepsin in N/10 HCl solution on the intestinal mucosa was reduced by lowering the temperature of the solution.

H. J. SIMS.

DRIVER, R. L. The inhibitory effect of mineral oil on the experimental production of ulcers. Am. J. Dig. Dis., 12: 395 (Dec.) 1945.

A series of 49 dogs were submitted to a study on isolated loops of intestine, to determine whether mineral oil decreases the severity of necrosis previously induced by pepsin in HCl. Loops of intestine were exposed to 0.1% pepsin in N/10 HCl solution, under a pressure of zero or 90 cm. H₂O. In each instance of those treated with mineral oil, the digestive action on the intestinal mucosa was inhibited.

H. J. SIMS.

ZUCKER, T. F., BERG, B. N., AND ZUCKER, L. M. Nutritional effects on the gastric

mucosa of the rat. I. Lesions of the antrum. J. Nutr., 30: 301 (Nov.) 1945. Evidence is adduced for the conclusion that in rats a rather early manifestation of calcium deficiency is found in the type of gastric lesion which occurs in the mucosa of the antrum. The changes consist of necrosis, hemorrhage, and epithelial hyperplasia. Addition of phosphate accentuates the lesions, while vitamin D administration definitely reduces their number. Thiamine or total B-complex deficiency will produce small lesions of the same type. However, while calcium increments in the diet abolish the lesions of thiamine deficiency, added thiamine has no preventive effect in calcium deficiency. The administration of neutralizing agents as such has no effect on the lesions, indicating the improbability that gastric HCl plays a role in their formation.

ARTHUR E. MEYER.

ZUCKER, T. F., BERG, B. N., AND ZUCKER, L. M. Nutritional effects on the gastric mucosa of the rat. II. Lesions of the fundus and rumen. J. Nutr., 30: 319 (Nov.) 1945.

While fundic lesions can be produced on deficient diets, their cause probably lies in inanition rather than any specific relation of a food factor to the structure of the fundic mucosa. The rat's rumen responds to some deficient diets with a quite reproducible reaction of hyperplasia and hyperkeratosis. While these lesions have been ascribed to deficiencies of both vitamin A and members of the B-complex, it is shown that they can be produced in the presence of ample vitamin A in the diet, and prevented on a totally B-deficient diet by increasing the (purified) casein content to 27%. The data suggest the possibility of a specific factor important for the prevention of lesions of the rumen which may be either an amino acid, labile to commonly employed methods of purifying casein, or an unknown factor associated with crude casein.

ARTHUR E. MEYER.

ABRAHAMSON, E. M. Hyperinsulinism as a factor in peptic ulcer. Am. J. Dig. Dis., 12: 379 (Nov.) 1945.

This clinician made a clinical study of hyper-

insulinism as a factor in peptic ulcer, with the following conclusions:

- (1) Hyperinsulinism can produce the symptoms of peptic ulcer, and chronic hypoglycemia often induces hyperperistalsis and spasm which may lead to ulcer.
- (2) The assumption that all cases of peptic ulcer have hyperinsulinism furnishes a ready explanation for the diabetic's comparative freedom from the other disease.
- (3) Chronic hypoglycemia probably has some etiological relation to ulcer, and the role of caffeine in producing hyperinsulinism suggests the re-evaluation of this alkaloid.

H. J. SIMS.

DRIVER, R. L., AND CARMICHAEL, E. B. The effect of bile salts on the experimental production of ulcer in the dog. *Am. J. Dig. Dis.*, 12: 378 (Nov.) 1945.

These investigators exposed isolated loops of intestine of anesthetized dogs to acid-pepsin solutions, both with and without bile salts. The solutions were in contact with the mucosa of the gut under zero or 90 cm. of water pressure, and at pH's of approximately 1.2 and 3.7. They observed that bile salts markedly inhibited the digestive action of pepsin on intestinal mucosa at pH of 1.25. At a pH of 3.7 there was no damage to the mucosa, regardless of hydrostatic pressure or the presence of bile salts.

H. J. SIMS.

SURGERY

CLAGETT, O. T. Transthoracic resection of lesions of the lower portion of the esophagus and the cardia of the stomach. *Proc. Staff Meetings Mayo Clinic*, 20: 506 (Dec.) 1945.

The transthoracic approach has made much easier the resection of the 10% of gastric cancers that arise in the cardia, and of the 33 to 35% of carcinomas of the esophagus arising in the lower third of this structure. This report is based on 57 cases operated on for lesions of the cardia and lower esophagus by means of the transthoracic approach; the operation was for malignancy in all but 3 instances. This operation permits adequate exposure for wide resection of these

lesions and their regional lymph nodes, and for maintenance of esophago-gastric continuity. Cardiac carcinoma may well extend up into the gullet, so that even complete gastric resection by the classical abdominal route will fail in removal of the entire lesion. The author does not feel that preliminary abdominal exploration need be performed, as operability can be determined by the transthoracic approach which carries no more risk than celiotomy. The author inveighs against preliminary jejunostomy as being unnecessary in any case considered fit for exploration and resection. Resection was performed in 33 of the 57 cases, 27 of them being for carcinoma of the cardia. Splenectomy was carried out in 14 of these cases and in 3 instances part of the distal end of the pancreas was removed as well. The author emphasizes that the transthoracic approach should be used when symptoms of dysphagia are present in lesions of the cardia.

FRANK NEUWELT.

CLOUT, H. M., AND KENNEY, F. R. Primary anastomosis in carcinoma of the colon. *New Eng. J. Med.*, 233: 799 (Dec.) 1945.

The authors present a study of 65 patients with cancer of the colon, including the rectosigmoid. In preparation of the colon for operation in unobstructed cases, one or two cleansing enemas are given on the day of admission; in addition, the patients receive sulfasuxidine in 2 gram doses, 5 times a day, for 3-4 days before operation. During this period, the patient is on a high calorie diet, rich in proteins and carbohydrates, with a low residue. The night before operation, Wangensteen drainage is started and continued postoperatively until peristalsis has been reestablished. In this series of 48 cases of resectable cancer of the colon, intestinal anastomoses were done in 34. In 7 patients, this was a secondary procedure where the growth was in the right colon. The cancer was present in the right colon in 10 instances; the transverse colon in 6; the splenic flexure in 6; the descending colon in 6; the sigmoid in 26, and the rectosigmoid in 11. The wide removal of the tumor and its lymph node-bearing mesentery, and immediate restoration of intestinal continuity is recommended. In 17 instances, the le-

sion was inoperable and palliative procedures were done. The over-all mortality for the entire series of 65 cases was 12%. The resection of the lesion with intestinal anastomoses is the method of choice. The authors state: "It is not a single factor that makes for better surgery in cancer of the colon, but better general surgical management in all its details."

IRVING GRAY.

PHYSIOLOGY: SECRETION

TEORELL, T., AND WERSALL, R. Electrical impedance properties of surviving gastric mucosa of the frog. *Acta Physiol. Scand.*, 10: 243 (Nov.) 1945.

In connection with some investigations on the formation of hydrochloric acid by the isolated surviving gastric mucosa of the frog, an interest arose concerning the applicability of electrical conductivity measurements as a means of recording changes in the electrolyte permeability. The alternating current impedance of the mucous membrane was examined over the frequency range 10-13,000 cycles per second. The results were expressed in terms of impedance locus diagrams.

In general it was found that different states of activity and external conditions had a marked influence on the impedance qualities, such as the "parallel resistance" and the "polarization angle." On the whole, it was found that strong stimulation (in connection with secretion, or electrical current flow) or injury (mechanical or chemical) in particular, affected the parallel resistance. Impedance quantities related to the polarization properties of the mucous membrane, i.e. the "polarization angle" and the "characteristic frequency," were sensitive to the exchange of sodium ions against potassium ions ("potassium effect").

The observations are discussed in the light of some current hypotheses. It is emphasized that great caution must be exercised when attempting to interpret the impedance quantities in terms of cell and tissue permeability.

ALBERT CORNELL.

BOYD, E. M., EARL, T. J., JACKSON, S., PALMER, B., AND STEVENS, M. Altera-

tions in the properties of dog hepatic bile with increasing age of the chronic biliary fistula. *Am. J. Physiol.*, 145: 186 (Dec.) 1945.

The 24 hour volume output of hepatic bile collected from 5 chronic biliary fistula dogs gradually rose until after the 12th week and then declined. The specific gravity and relative viscosity steadily declined throughout. The daily output of total solids remained fairly constant until toward the end of the experiment, but the composition of the total solids underwent considerable change which could be divided into three periods. In the first period, immediately after some three weeks of fistulous drainage, there was a marked decrease in the output of total fatty acids, bilirubin and bile salts with an increase in the output of sodium, potassium and chlorides. In the second period, from the 4th to the 12th weeks of biliary drainage a further gradual increase in the output of sodium, potassium, and chlorides, and a continued decline in the output of total fatty acids occurred. In the third period, after the 12th week and just before the death of the animals, there was a decline in the volume output of bile and in the amount of total solids—sodium, potassium, chlorides, bilirubin, bile salts, total cholesterol and ester cholesterol. No marked or consistent changes in the average daily output of inorganic phosphate or free cholesterol were observed.

ARTHUR E. MEYER.

MUNRO, M. P., AND THOMAS, J. E. The number and relative concentrations of protein constituents of canine pancreatic juice as determined by electrophoresis. *Am. J. Physiol.*, 145: 140 (Dec.) 1945.

Pancreatic juice obtained from dogs under the influence of various stimuli has been subjected to electrophoretic fractionation. In sodium bicarbonate buffer at pH 8.2, the juice separates into 4 or 5 components, depending on the dog under observation, but independent of the stimulus used or the protein concentration of the juice. In sodium diethylbarbiturate buffer at pH 8.6, an additional boundary generally appears.

The relative proportions of the several components tend to remain fairly constant.

Arthur E. Meyer

METABOLISM AND NUTRITION

GOLDZIEHER, M. A., REIMER, N. A. AND GOLDZIEHER, J. W. Metabolic abnormalities in obesity: a statistical survey. *Am. J. Dig. Dis.*, 12: 387 (Dec.) 1945.

These clinicians reported their findings in 1000 consecutive unselected cases of obesity, and compared these findings with another group of 100 consecutive obese cases in which a clinical diagnosis of pituitary disease was made. Their study included: basal metabolism, specific dynamic action of proteins, fasting-blood sugar, blood uric acid, lymphocytic count, 24-hour urine volume, NaCl excretion, and salt tolerance. The mean basal metabolic rate was lower in the obese and significantly lower in pituitary obesity. The highest specific dynamic action appeared in those of the hypothyroid type. The mean of the fasting blood sugar in the obese was normal but the mean blood sugar in the pituitary and in juvenile obesity was increased. A higher mean percentage was obtained in pituitary obesity. Lower 24 hour urine volume and diminished salt excretion were characteristic in both types of obesity. Lymphocytosis was a constant finding in both types of cases.

H. J. Sims.

ANATOMY

RICHIE, C. A. The innervation of the pancreas. *J. Comp. Neurol.*, 83: 223 (Dec.) 1945.

The pancreas is innervated by sympathetic and parasympathetic nerves and also by visceral afferent fibers. The sympathetic preganglionic nerves traverse the splanchnic nerves; the parasympathetic preganglionic fibers traverse the vagi. In order to determine whether secretory fibers or vasmotor changes produced secretion upon stimulation of splanchnic and vagal nerves, the author produced nerve degeneration in 4 series of operations upon cats: viz., (1) celiac ganglia were removed to degenerate all nerve fibers passing through or originating therein, (2) vagi were severed at the lower level of the esophagus to degenerate parasympathetic

preganglionic and sensory vagal fibers, (3) splanchnic nerves were severed bilaterally to degenerate afferent and sympathetic pre-ganglionic fibers, (4) celiac ganglia were removed and vagi were severed. Operated animals were allowed to live 3 weeks to assure complete degeneration.

The author found myelinated and non-myelinated fibers present in the ratio of 1 to 19 just peripheral to the celiac ganglia. Sympathetic preganglionic fibers terminate exclusively in the celiac ganglia and aberrant ones along the pancreatic blood vessels. Parasympathetic preganglionic fibers terminate in intrinsic pancreatic ganglia. Sympathetic postganglionic fibers are distributed solely to the pancreatic blood vessels where they form perivascular plexuses. Parasympathetic postganglionic fibers course along the blood vessels in small bundles and distribute ultimately to the acinar and islet cells. Single nerve fibers may effect contact with both acinar and islet cells. The nerve fibers send off fine branches with abundant knob-like enlargements. Some terminal loops occur on the surface of acinar cells. Smooth muscle around the ducts is supplied by parasympathetic postganglionic fibers. Sensory end-organs in the pancreas are the Pacinian corpuscles.

E. N. Collins.

MENTEN, M. L., AND DENNY, H. E. Duplication of the veriform appendix, the large intestine and the urinary bladder—report of a case. *Arch. Path.*, 40: 345 (Nov.-Dec.) 1945.

The authors report the case of a Negro boy, 4 months old, which revealed at autopsy the duplication of the entire large intestine with associated doubling of the appendix and the bladder. They discuss the theories of the genesis of intestinal anomalies, and conclude that this occurrence of a double bladder and double large intestine with two separate veriform appendices indicates that the anomalous morphogenesis began before the separation of the urorectal septum, which begins in an embryo of 5.3 mm. length. The formation of mucoid vesicles as a method of origin of intestinal duplications occur, according to Bremer, in embryos of 6 weeks of age or 10 mm. of length, and they are found

almost exclusively in the small bowel. Thus the latter theory cannot hold in the present case. Reference is made to the organizer concept for morphogenesis as advanced by Spemann and by Needham, as another possible explanation for such anomalies.

N. W. JONES.

MISCELLANEOUS

Co Tui. The value of protein and its chemical components (amino acids) in surgical repair. *Bull. N. Y. Acad. Med.*, 21: 631 (Dec.) 1945.

The role of protein nutrition in repair is discussed under three headings: (1) wound healing, (2) maintenance of tissue integrity, and (3) convalescence. Protein deficiency plays an important role in wound dehiscence. The role of protein nutrition in maintaining tissue integrity was suggested by observations on non-neurologic cases of bed sores. When the nitrogen balance was reversed from negative to positive, the bed sores healed promptly. By determining body weight, nitrogen balance, and muscular endurance with the bedside ergograph, the author studied protein nutrition in convalescence from burns, gastrectomy, herniotomy, cholecystectomy, and peptic ulcer. From these studies, the author concludes that a patient can become protein-deficient as a result of inadequate intake or increased nitrogen output, or a combination of these two factors. The increased nitrogen output may be due to increased metabolic loss and to loss through exudates. The ceiling of nitrogen intake in natural food is low and consequently natural food is often inadequate to replenish the increased protein loss in disease and injury. Convalescence can be shortened, and strength and weight conserved, by full caloric and nitrogen replacement immediately postoperatively. There may be a critical change of nitrogen intake for each disease category. The protein hydrolysates, by raising the ceiling level of nitrogen intake, are indispensable in many disease conditions and can be used with greater elasticity than natural foods. A new treatment for peptic ulcer has been evolved as a result of these studies. Prote-

ins are essential to wound healing, to the maintenance of tissue integrity, and, from present indications, to expeditious convalescence. Protein deficiency endangers all three.

ALBERT CORNELL.

SWENSON, O., AND LADD, W. E. Surgical emergencies of the alimentary tract of the newborn. *New Eng. J. Med.*, 233: 660 (Nov.) 1945.

The authors discuss such emergencies as esophageal atresia, omphalocele, diaphragmatic hernia, intestinal atresia or stenosis, meconium ileus, midgut volvulus, and imperforate anus. In the past 6 years, there have been 64 cases of esophageal atresia. In 21, direct anastomoses were accomplished with 5 survivals. In the remaining 43, multiple stage operations were performed. Twenty-four patients with congenital diaphragmatic hernia have been operated on with only 5 deaths. Following institution of Wangensteen suction to combat abdominal distention, infants with intestinal stenosis or atresia may be operated on within several days after birth. No progress has been made in dealing with meconium ileus. This disease, caused by pancreatic insufficiency, is still uniformly fatal. To date, there have been 30 infants with midgut volvulus operated upon, with only 4 deaths. The authors point out that plain X-ray films of the chest and abdomen in the surgical emergencies of the alimentary tract of the newborn will, in most cases, give sufficient information for a definite diagnosis. If barium is used in an infant who is vomiting, there is always the danger of aspiration with serious resulting pneumonia. The use of lipiodol in patients with esophageal atresia is as satisfactory as barium and far less dangerous.

IRVING GRAY.

WEINSTEIN, E. A., AND STEIN, M. H. Psychogenic disorders of the upper gastrointestinal tract in combat personnel. *War Med.*, 8: 365 (Nov.-Dec.) 1945.

The problem of gastric disorders among combat soldiers in the Mediterranean Theatre has been primarily psychiatric in nature.

Because of the large number of these neurotic cases, accurate diagnosis and understanding were very important. This neurosis in combat is engendered by the battle situation regardless of the preexistence of such symptoms in civilian life.

Clinically, these patients are divided into three groups on the basis of the degree of anxiety and the manner in which it is expressed. The first group reveal the usual features of the combat-induced anxiety state, with complaints of nervousness, fear, tremor, insomnia, weakness, fatigue, and headache. The second type of patient has little overt anxiety but many complaints about his stomach. The third and smallest group comprises the hysterics, manifested principally by persistent vomiting. Psychodynamically, these symptoms have their genesis in a system based on anxiety and hostility. Symbolically they represent the rejection of food given the soldier by the army-parent.

Characteristic of neurotic gastrointestinal symptoms is their failure to improve to any extent with hospitalization, medication, diet, and rest. The differential diagnosis of neurotic gastric disturbances is almost always possible on clinical and psychiatric grounds alone and only rarely are Roentgen and extensive laboratory studies necessary. The two conditions which offer the most difficulty are peptic ulcer and hepatitis. The principles of treatment include minimal hospitalization; thorough recording of history and examination; and psychotherapeutic measures which include explanation, reassurance, and improvement of attitudes. All treatment is conditional on the development of the proper patient-physician relationship.

MICHAEL W. SHUTKIN.

TICE, G. M. The unusual in gastrointestinal roentgenology. *Ann. Int. Med.*, 23: 837 (Nov.) 1945.

A sound background of pathology is necessary for the roentgenologist. Several examples of relatively rare gastro-intestinal pathological processes are presented. An esophageal-pharyngeal diverticulum occurs on the posterior wall at the junction of the pharynx and esophagus. The esophagus roentgenologically emerges high on its anterior surface. Esophageal and gastric varices can be demonstrated by having the patient lie in a supine or oblique supine position using a small quantity of a moderately thick barium solution. A beaded defect is noted where the veins are most numerous. Achalasia or cardiospasm is differentiated from carcinoma by the use of amyl nitrite perls in doubtful cases. Hiatal hernia is best demonstrated by having the patient supine or sometimes prone. After the barium meal the patient is placed in the Trendelenburg position and the Valsalva maneuver is carried out, which allows the herniation to be visualized. The dependable roentgen sign for the presence of a bezoar is a filling defect in the barium-filled stomach which can be moved about.

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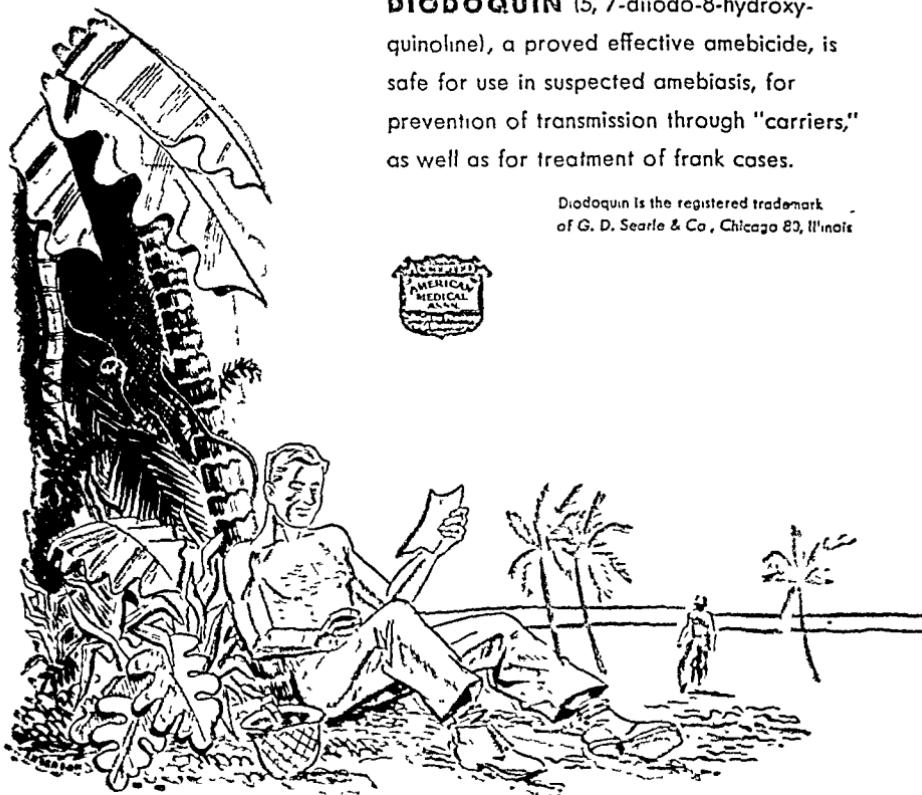


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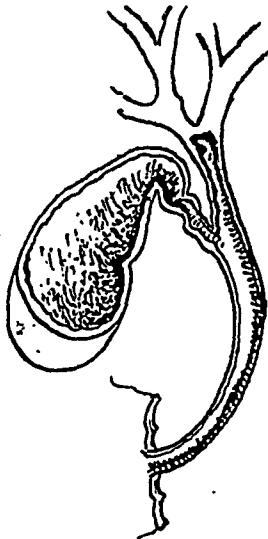
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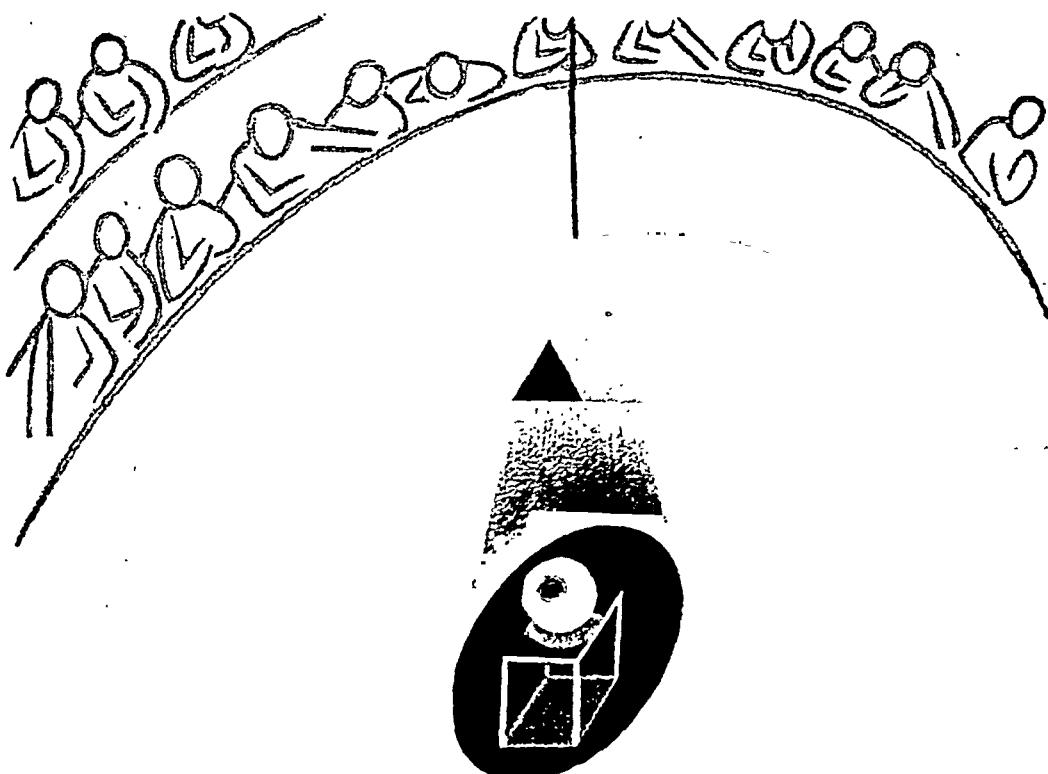
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* Waldapfel, R.: Pharyngoesophageal diverticulum, Eye, Ear, Nose & Throat Month., 24: 579 (Dec.) 1945.

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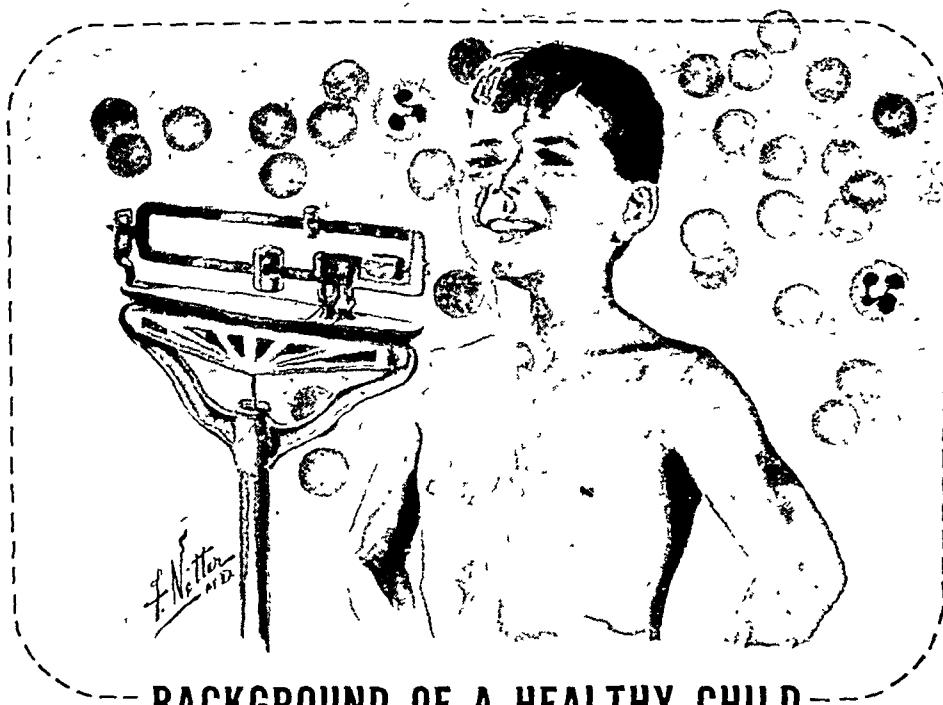
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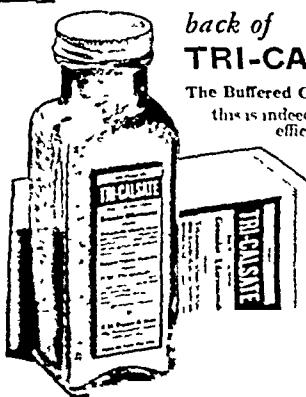
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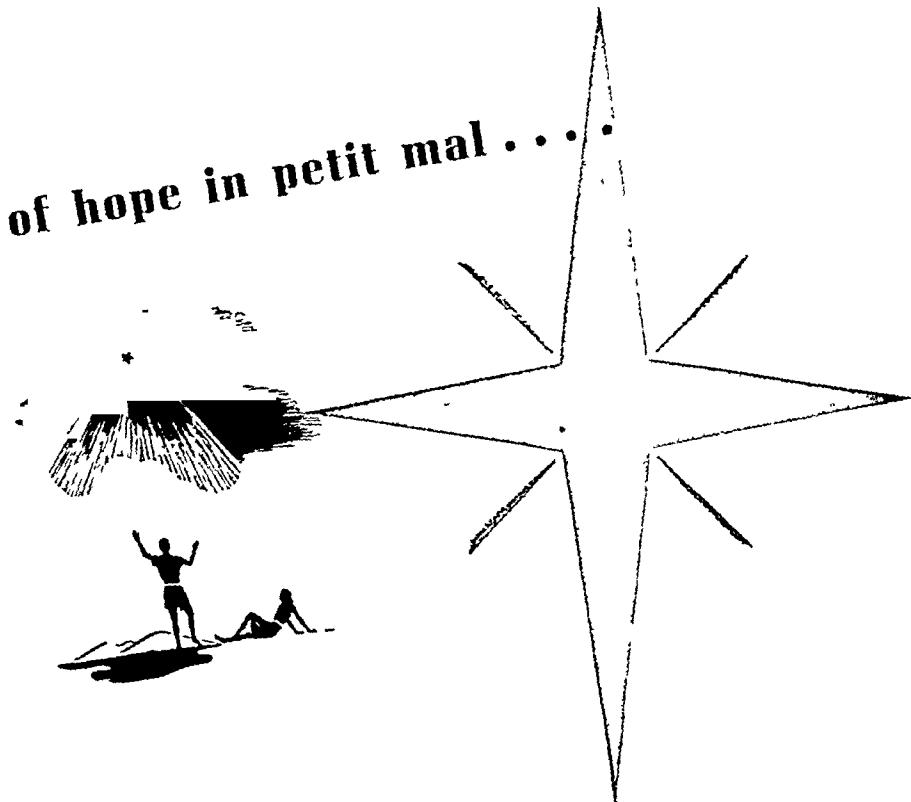
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Lemon, W. G. (1955). Petit Mal Epilepsy. Their Treatment with Tridione. J. Amer. Med. Assn., 159: 1049, Decem. 25.

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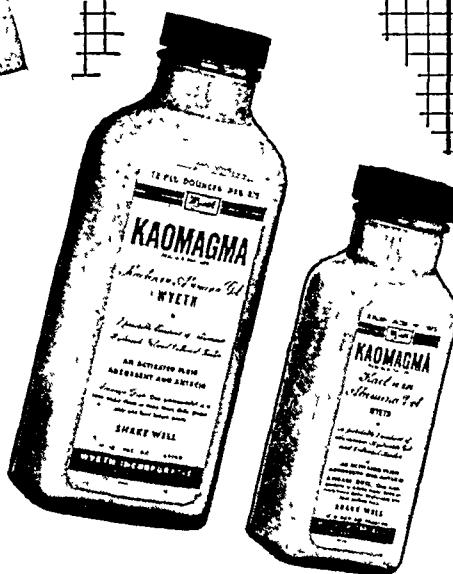
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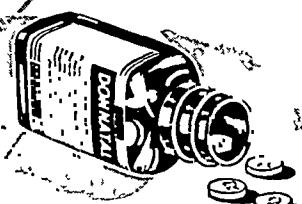
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VOLUME 7, NUMBER 6

DECEMBER, 1946

GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

TABLE OF CONTENTS

The Effect of Transthoracic Vagotomy upon the Clinical Course of Patients with Peptic Ulcer. JULIAN M. RUFFIN, M.D., KEITH S. GRIMSON, M.D., AND R. CATHCART SMITH, M.D.	599
The Insulin Test for the Presence of Intact Nerve Fibers After Vagal Operations for Peptic Ulcer. FRANKLIN HOLLANDER, PH.D.	607
Discussion on Symposium on Peptic Ulcer with Particular Reference to Vagotomy. KEITH S. GRIMSON, M.D., JULIAN M. RUFFIN, M.D., AND FRANKLIN HOLLANDER, PH.D.	615
The Effectiveness of Parenterally Administered "Enterogastone" in the Prophylaxis of Recurrences of Experimental and Clinical Peptic Ulcer. HARRY GREENGARD, PH.D., M.D., ARTHUR J. ATKINSON, M.S., M.D., M. I. GROSSMAN, PH.D., M.D., AND A. C. IVY, PH.D., M.D.	625 ✓
Intestinal Parasites in Service Personnel in the South Pacific: with Special Reference to the Incidence and Treatment of Strongyloidiasis. JOHN H. WILLARD, M.D.	650
Surgery in Acute Pancreatitis. ROBERT ELMAN, M.D.	656
Etiology of Cholecystitis. MARTIN E. REHFUSS, M.D.	665
CLINICAL PATHOLOGICAL CONFERENCES AND INSTRUCTIVE CASES	
Cholecystitis and Cholelithiasis in Identical Twins. JAMES TESLER, M.D.	685
Case Report. MANFRED KRAMER, M.D.	687
EDITORIALS	
Vagotomy in the Treatment of Ulcer. JULIAN RUFFIN	692
Anorexia Nervosa, A Mental Disease. W. C. A.	693
COMMENT	
The Virus of Lymphogranuloma Venereum. W. C. A.	696
A Drug Which Doubles the Analgesic Effects of Opium and its Derivatives. W. C. A.	697
BOOK REVIEWS	
Preventive Medicine and Public Health	698
Medical Biochemistry	698
Chemistry of Food and Nutrition	698
Men Without Guns	698
ABSTRACTS	
	699

For Instructions to Authors and the address of the Editor see the advertising section following the Abstracts.

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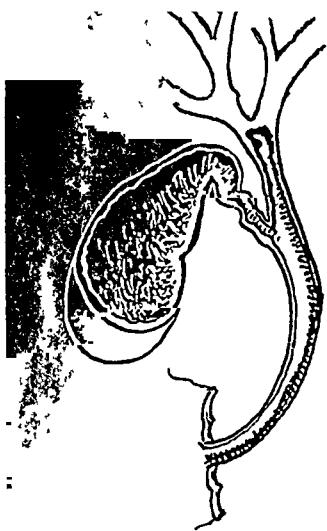
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| 1. Gastroenterology 3 54, 1944 | 3. J. Lab. and Clin. Med. 18 1016, 1933 |
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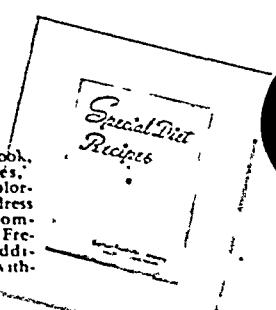
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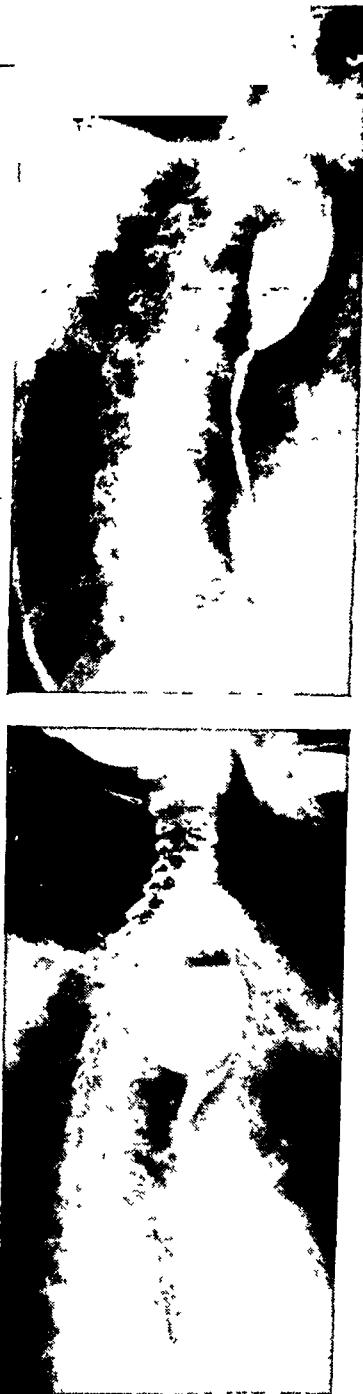
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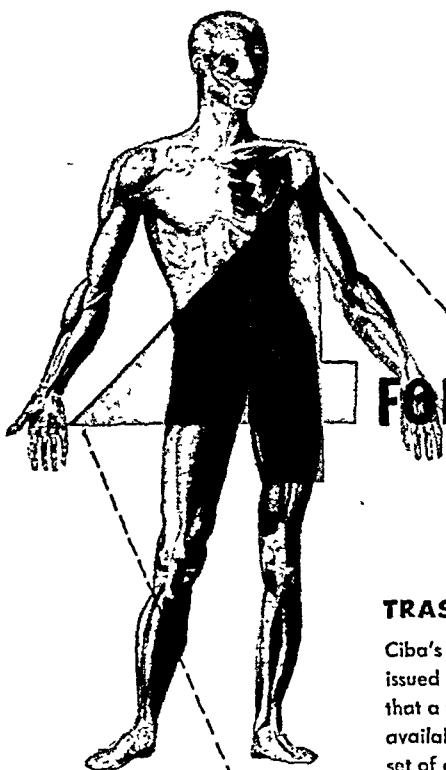


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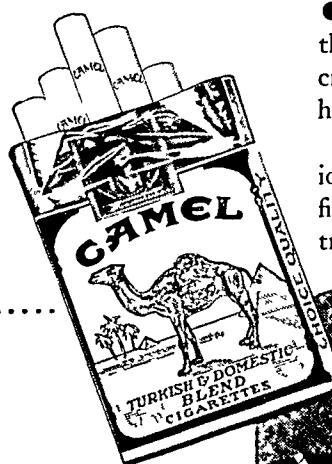
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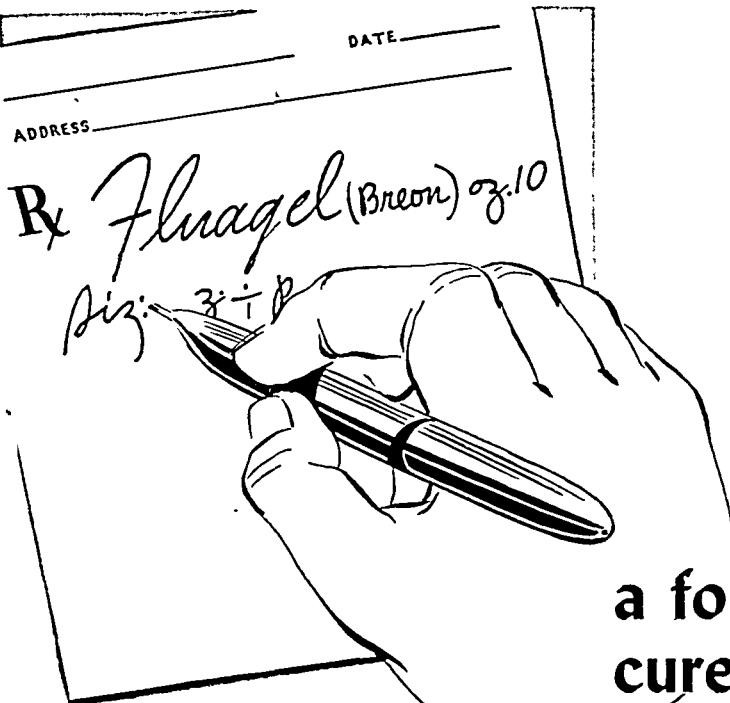
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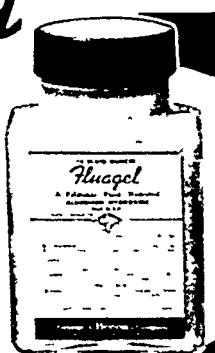
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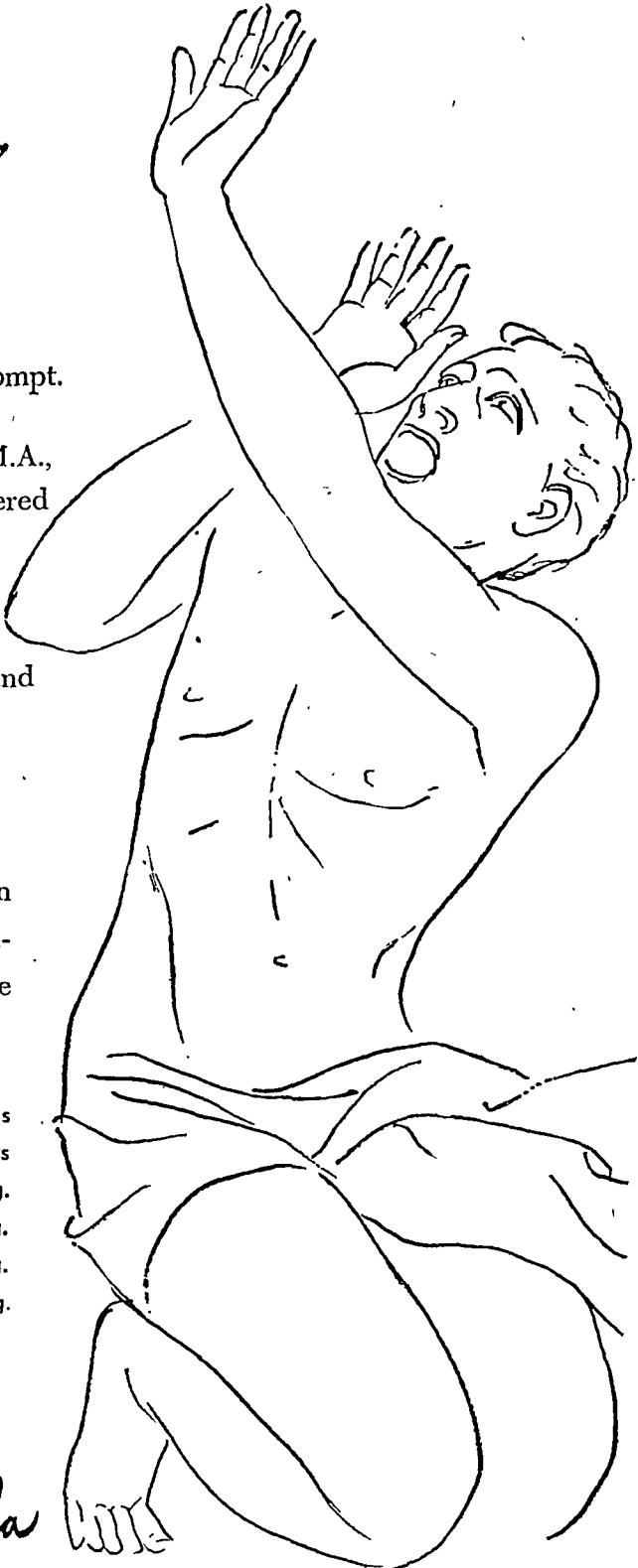
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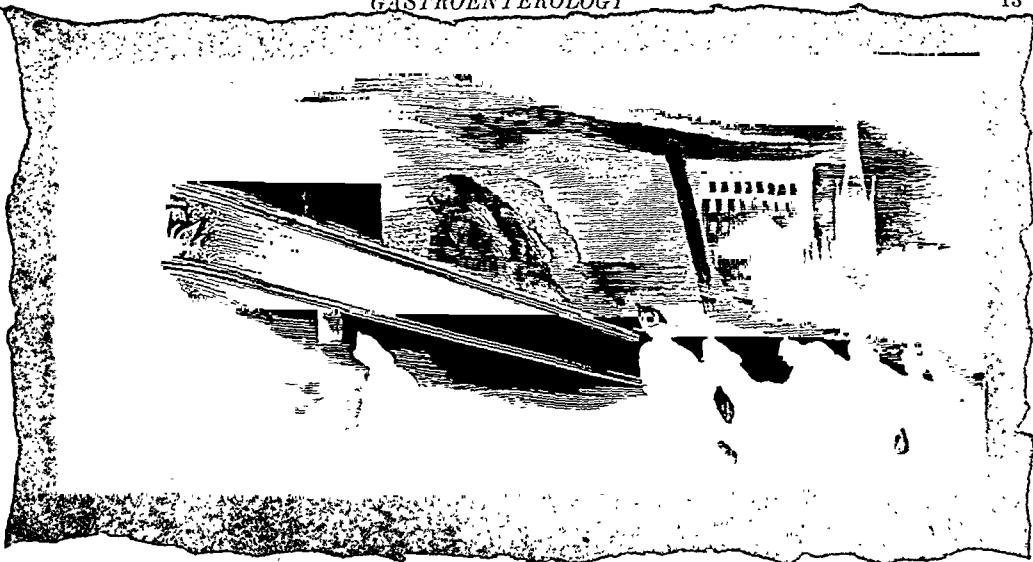
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- 1 Meyer Spier and Newell Arch. Int. Med. 61:171, 1940
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THE EFFECT OF TRANSTHORACIC VAGOTOMY UPON THE CLINICAL COURSE OF PATIENTS WITH PEPTIC ULCER^{1, 2}

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INTRODUCTION

The exact etiology of peptic ulcer has never been established, nor have the results of conventional therapy proven entirely satisfactory. Certain patients have required surgery because of intractable pain, obstruction, hemorrhage or perforation, or because they have been unable or unwilling to follow a thorough medical program.

The operations usually performed have been gastroenterostomy or subtotal gastric resection. Recently a great deal of interest has developed in resection of the vagus nerves and their branches about the lower esophagus in the treatment of peptic ulcer. The theoretical basis for this operation, which was devised by Dragstedt (1), and the results of this procedure have been discussed by him and by others (2-8). The purpose of this communication is to report the effect of transthoracic vagotomy upon the clinical course of a series of patients having peptic ulcer.

MATERIAL

This report is based upon a study of thirty patients at Duke Hospital who have had a transthoracic vagotomy for peptic ulcer. Each patient had a chronic or recurrent ulcer which had failed to respond satisfactorily to previous medical or surgical treatment. Twenty-four of these had severe and intractable pain, and fourteen gave a history of repeated massive hemorrhage. The majority of them were partially or completely disabled because of their ulcer. One or more operations had been performed in fifteen patients, including gastroenterostomy, gastric resection, or closure of a perforation.

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² We wish to acknowledge the assistance of Doctor George J. Baylin, Department of Radiology, and o^r ylor, Department of Biochemistry.

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The duration of ulcer symptoms ranged from three to thirty-five years, the average being eleven. Twenty-four patients had a duodenal ulcer, five a marginal ulcer, and one both a gastric and a duodenal lesion. There was one white woman and one colored man, the remainder being white males. The follow-up period of the patients reported in this series has ranged from one and one-half to twenty-one months, the average being nine.

RESULTS

Since vagotomy, every patient has been relieved of ulcer symptoms and has been able to consume a full and unrestricted diet without ill effect. Two patients who were definitely psychiatric problems before operation have not entirely recovered. They have both continued to feel "weak and nervous" and have been unable or unwilling to resume a normal life, although they have been relieved of their original ulcer symptoms. The remainder of the patients have made a complete clinical recovery to date (Table I).

Ulcer Pain. Ulcer pain had occurred in every patient at some time before vagotomy and was present at the time of operation in twenty-six. *In every case the pain was completely relieved immediately after vagotomy and has not recurred.*

Hemorrhage. Fourteen patients gave a history of repeated massive hemorrhage. In thirteen of these there has been no recurrence of bleeding since operation. The fourteenth patient, who had a massive hemorrhage two weeks before vagotomy, vomited a small amount of blood three weeks after operation. However, his hemoglobin and red count did not drop appreciably, nor did he have a tarry stool. He has been followed for six months since this time and has had no further evidence of bleeding.

Vomiting. Twenty-four patients gave a history of vomiting and in sixteen this was severe at the time of hospitalization. Since discharge from the hospital vomiting has occurred occasionally in three patients. This was usually associated with over-eating and for the most part was of no particular consequence.

Appetite. All of the patients reported in this series had a normal appetite after vagotomy. They experienced the usual hunger sensations when the stomach was empty, as well as a feeling of satiety after a full meal.

Effect of vagotomy upon other gastro-intestinal symptoms

Epigastric fullness. A feeling of fullness and distention in the epigastrium often followed vagotomy. This was always associated with gastric retention which could be demonstrated by x-ray or by aspiration. Occasionally patients were able to obtain relief by abdominal massage while lying on the right side. In general, this symptom was of no particular consequence and subsided within three to four weeks after operation.

TABLE I

PATIENT	AGE	SEX	LOCATION OF ULCER	DURATION OF SYMPTOMS	INTERVAL SINCE OPERATION	ULCER PAIN		HEMORRHAGE	DIARRHEA	DISABILITY
						Before	After			
1	36	M	Duodenal	6	21	++	+	•	++	*
2	36	M	Duodenal	14	20	+++	++	++	++	++
3	46	M	Duodenal	20	17	+++	++	++	++	++
4	42	W	Duodenal	11	16	+++	++	++	++	++
5	41	W	Marginal	12	13	+++	++	++	++	++
6	38	W	Duodenal	7	13	+++	++	++	++	++
7	35	W	Duodenal	8	13	+++	++	++	++	++
8	38	C	Duodenal	6	13	+++	++	++	++	++
9	29	W	Duodenal	15	13	+++	++	++	++	++
10	41	W	Duodenal	3	12	+++	++	++	++	++
11	63	M	Duodenal	35	12	+++	++	++	++	++
12	44	W	Duodenal	6	11	+++	++	++	++	++
13	28	M	Duodenal	4	10	+++	++	++	++	++
14	30	W	Duodenal	7	8	+++	++	++	++	++
15	29	M	Duodenal	10	7	+++	++	++	++	++
16	48	W	Gastric & Duodenal	3	7	+++	++	++	++	++
17	46	W	Duodenal	10	6	+++	++	++	++	++
18	31	W	Duodenal	3	6	+++	++	++	++	++
19	36	W	Duodenal	6	6	+++	++	++	++	++
20	32	W	Duodenal	5	5	+++	++	++	++	++
21	31	W	Duodenal	10	5	+++	++	++	++	++
22	35	W	Duodenal	10	4	+++	++	++	++	++
23	46	W	Duodenal	19	4	+++	++	++	++	++
24	52	W	Duodenal	15	3	+++	++	++	++	++
25	58	W	Duodenal	12	3	+++	++	++	++	++
26	51	W	Duodenal	13	3	+++	++	++	++	++
27	64	M	Marginal	20	3	+++	++	++	++	++
28	27	W	Duodenal	10	1	+++	++	++	++	++
29	61	W	Marginal	16	1	+++	++	++	++	++
30	49	M	Marginal	12	1	+++	++	++	++	++

* A psychopathic personality who had a colitis before vagotomy.

† Vomited a small amount of blood three weeks after operation; none since.

Constipation and diarrhea. Although constipation was common before vagotomy, since operation this has not been observed in a single case. On the other hand, a mild, transient diarrhea developed in twelve patients. This varied from a single loose stool to four or five movements per day, and occasionally was accompanied by lower abdominal distress. This complication appeared shortly after operation and lasted for a few days to several weeks, usually subsiding without treatment. A severe intermittent diarrhea developed in one patient, who was one of the psychiatric problems referred to above. There was no relationship between the development of diarrhea and achlorhydria, either in the fasting sample or after histamine (Table II).

Miscellaneous gastric sensations. Distention of the stomach after vagotomy was perceived in all patients tested, either by inflation with air during gastroscopy or by distention with fluid. Traction upon the stomach by introducing the gastroscope beyond its usual depth invariably was accompanied by a sensation of stretching, pulling, or distress. Sensations of heat and cold were

TABLE II

	DIARRHEA	NO DIARRHEA
Fasting samples		
Free HCl present in all specimens.....	0	3
Free HCl absent in all specimens.....	3	5
Free HCl present intermittently.....	9	8
After histamine		
Free HCl present in all specimens.....	7	9
Free HCl absent in all specimens.....	0	1
Free HCl present intermittently.....	0	0

perceived by all of the six patients who were tested. This was done by introducing hot or cold water into the stomach by nasal tube. However, the sensation was both epigastric and substernal and it was difficult to determine whether it arose from the esophagus or from the stomach itself.

Abdominal pain. Two patients developed an acute abdomen several months after vagotomy. One had an acute cholecystitis and the other a strangulated Meckel's diverticulum. Both of these patients experienced the usual pain associated with these diseases.

Body weight. With one exception, all patients followed for more than three months have maintained or gained weight. The maximum gain was forty-eight pounds and the average for the twenty-two patients followed was eighteen.

Introduction of HCl into the stomach

Three hundred cc. of 0.5% HCl were introduced into the stomach by nasal catheter in three patients (9). This procedure was carried out twice in each

case before vagotomy. After vagotomy the test was performed as soon as the patient had recovered from the anaesthesia and on several subsequent occasions. One patient had an active duodenal ulcer, the second an active marginal ulcer, and the third had had repeated massive hemorrhages, but the ulcer was thought to be inactive at the time of operation. The first two patients experienced typical ulcer pain before vagotomy, but after operation the introduction of acid did not produce pain in either case.⁴ In the third patient this procedure caused no pain either before or after vagotomy. As a control experiment, three hundred cc. of water were introduced into each of the three patients. This caused a slight sensation of fullness without pain and was withdrawn before the acid was introduced. Three other patients were tested with acid several months after operation. One of these had had a marginal ulcer and two a duodenal. In all three, no discomfort whatever was noted.

TABLE III
Effect of vagotomy upon free HCl in fasting samples

No free HCl after vagotomy.....	12
No free HCl after vagotomy, but gradual return of acid.....	11
Definite lowering of free HCl.....	3
No effect upon free HCl.....	4
	—
Total.....	30

Effect upon gastric acidity

Detailed studies of the effect of vagotomy on the volume and acidity of the gastric secretion have already been reported (7). Studies on the patients in this series, therefore, will be summarized only. The volume of the secretion of the fasting stomach was reduced roughly by half. Immediately after vagotomy and in some cases extending over a period of four months there was no free HCl in any of the fasting samples in twelve patients. Eleven other patients developed achlorhydria immediately after operation, but after a period of several months there was a return of free HCl, though not to preoperative levels. In three patients there was a definite lowering of gastric acidity, while in four no effect whatever was noted. Thus, there were seven patients who never developed achlorhydria after operation (Table III). In general, values for combined acid have definitely increased after vagotomy. The insulin hypoglycemia test (10, 11) was employed in fourteen patients. After vagotomy there was a decrease to absence of free HCl in all patients tested.

⁴ Two other patients, not reported in this series, were also tested with HCl. One had a duodenal and the other a gastric ulcer, both of which were active. The results of these tests were similar to those described above.

Effect upon motility

Motility. X-ray studies were conducted in twenty-eight patients within a short time after vagotomy. With the exception of those who had a previous gastroenterostomy or resection, all but one had marked delay in emptying of the stomach. This was usually associated with moderate to marked dilatation and decrease or absence of peristalsis. In one patient with a gastric ulcer the stomach was reported as being normal in size with relatively normal activity.

Retention. After the barium meal, twenty patients had a six-hour retention and in ten of these this was reported between ninety and one hundred per cent. Eight patients had no retention, but seven of these had had previous gastric surgery, such as a gastroenterostomy or partial resection. This retention was accompanied by a feeling of fullness in the upper abdomen and occasionally by regurgitation of food. In three patients the retention was so marked as to require relief by surgery. In the remaining eighteen, the retention gradually subsided and after several months the stomach apparently was emptying satisfactorily.

Observations at laparotomy following vagotomy

Two patients had a pyloroplasty eleven and fourteen days after vagotomy, respectively, because of obstruction. Examination revealed scar tissue without active inflammation in one and moderate inflammatory reaction and edema in the other. No definite ulceration could be demonstrated in either. Gastroenterostomy was performed on a third patient twenty-six days after operation because of retention. Examination revealed a large stomach with obstruction in the first portion of the duodenum by edematous inflammatory reaction and scar tissue. A fourth patient was explored three months after vagotomy and found to have a strangulated Meckel's diverticulum. One year later he was again operated upon because of intestinal obstruction. The stomach and duodenum were examined during both operations and no evidence of ulcer found.

Complications

The major complication of vagotomy has been dilatation and delayed emptying of the stomach as described above. Less serious and transient complications have resulted from the thoracotomy (12). Accumulation of fluid in the left pleural cavity occurred in all patients in this series, but not in sufficient quantity as to require aspiration. Atelectasis developed in five patients and another five had a mild pneumonia which responded promptly to chemotherapy. The pain at the site of the operation was often severe during the first few days after vagotomy and required opiates for relief. Infection of the

pleural cavity or of the operative wound did not occur. Continuous sterile drainage is now being employed routinely during the first several days after vagotomy.

DISCUSSION

Transthoracic vagotomy has resulted in complete relief of ulcer symptoms to date in each of thirty patients who had a chronic or recurrent peptic ulcer. In every case the ulcer had been present over a period of years and had failed to respond satisfactorily to conventional treatment. With the exception of the two cases described previously as psychiatric problems, their entire outlook on life and manner of living has changed from one of semi-invalidism to that of a normal existence. They are now able to consume a full and unrestricted diet without ill effect.

As a rule, varying degrees of gastric retention developed in almost every patient who did not have a gastroenterostomy or a gastric resection prior to vagotomy. In three patients this was so severe as to require subsequent gastroenterostomy. In two patients with obstructive symptoms before operation a gastroenterostomy was performed at the time of vagotomy to prevent this complication. There is some evidence that gastric motility returns toward normal along with subsidence of dilatation. If there is any clinical or radiologic evidence of retention, pyloroplasty or gastroenterostomy is definitely indicated, either prior to or at the time of vagotomy.

A minor, but interesting, complication of vagotomy has been the development of a mild, transient diarrhea. There was no correlation between the diarrhea and the presence or absence of free HCl and the explanation for this phenomenon is not yet apparent.

In general the total volume of gastric secretion was markedly reduced by vagotomy, as well as the free HCl content of the fasting stomach. While most of the patients showed a decrease or absence of free HCl after vagotomy, yet in four patients it had no demonstrable effect on the free HCl levels.

One of the most striking results of vagotomy is the immediate, complete, and apparently permanent relief of pain. It would seem that there are four possible explanations for this phenomenon (1, 7, 8): 1) Effect of anaesthesia (ethylene ether); 2) Interruption of sensory pathways; 3) Decrease or absence of free HCl; 4) Decrease or absence of peristaltic activity of the stomach. The effect of anaesthesia is transient and it would seem that the pain would certainly recur. It is difficult to prove that the pain pathways have not been interrupted. However, it is generally believed that visceral pain is carried by the splanchnic nerves. Furthermore, distention, traction, and probably heat and cold are perceived by the patient after vagotomy. It is improbable that the relief of pain is due only to the decrease or absence of HCl because in four pa-

tients who had normal free HCl levels after vagotomy, the pain was immediately relieved and has not recurred. Also, introduction of free HCl immediately after vagotomy and on several occasions later in two patients in this series and in two others, not included in this report, caused no pain; whereas, each had experienced typical pain by this procedure before operation.

Dilatation and delayed emptying of the stomach were a constant finding after vagotomy, except in those patients who had a previous gastroenterostomy or gastric resection. The most striking effect of vagotomy in this series of patients was the reduction or absence of gastric motility, so much so that one wonders if this is not the most likely explanation for the immediate relief of pain and subsequent healing of the ulcer.

CONCLUSIONS

1. Thirty patients who have had a transthoracic vagotomy for peptic ulcer have experienced complete relief of ulcer symptoms to date.
2. The most constant effect of vagotomy is the reduction or absence of gastric motility. In those patients who have not had a previous gastroenterostomy, retention and dilatation of the stomach are likely to occur.
3. Decrease in volume and acidity of the gastric secretions usually follows vagotomy.
4. The relief of pain following vagotomy probably is the result of decreased motility rather than a lowering of gastric acidity.
5. The time interval is too short to draw any conclusions as to the permanent or lasting value of the procedure.

REFERENCES

1. DRAGSTEDT, L. R.: Ann. Surg., 122: 973, 1945.
2. DRAGSTEDT, L. R.: Arch. Surg., 44: 438, 1942.
3. DRAGSTEDT, L. R., AND OWENS, F. M.: Proc. Soc. Exp. Biol. and Med., 53: 152, 1943.
4. DRAGSTEDT, L. R., PALMER, W. L., SCHAFER, P. W., AND HODGES, P. C.: Gastroenterology, 3: 450, 1944.
5. DRAGSTEDT, L. R., AND SCHAFER, P. W.: Surgery, 17: 742, 1945.
6. THORNTON, T. F., JR., STORER, E. H., AND DRAGSTEDT, L. R.: J. A. M. A., In Press.
7. GRIMSON, K. S., TAYLOR, H. M., TRENT, J. C., WILSON, D. A., AND HILL, H. C.: South. Med. Jour., In Press.
8. MOORE, F. D., CHAPMAN, W. P., SCHULZ, M. D., AND JONES, C. M.: New England Jour. Med., 234: 241, 1946.
9. PALMER, W. L.: Arch. Int. Med., 38: 694, 1926.
10. WEINSTEIN, V. A., COLP, R., HOLLANDER, F., AND JEMERIN, E. E.: Surg., Gynec. and Obst., 79: 297, 1944.
11. BABKIN, B. P.: Am. J. Dig. Dis., 5: 467, 1938.
12. GRIMSON, K. S.: Surg. Clin. North Am., In Press.

THE INSULIN TEST FOR THE PRESENCE OF INTACT NERVE FIBERS AFTER VAGAL OPERATIONS FOR PEPTIC ULCER¹

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INTRODUCTION

This symposium is concerned with the physiological and clinical consequences arising from the complete interruption of vagal communications to the stomach. The experiences of the Gastroenterology Research Group at our Hospital (7) and of Dr. Dragstedt and his associates (6) have demonstrated that attempts at *total* (bilateral) vagotomy in patients with peptic ulcer may not always be successful, because of the complexity of the distribution of vagal branches in the lower thoracic and the upper abdominal regions. Hence, no results of *total* vagotomy operations are significant unless it has been established by physiological as well as surgical evidence that all of the fibers of the vagus nerve have been intercepted. In order to provide such physiological evidence, a test has been devised in this Laboratory, and it is the purpose of this report to describe its physiological foundations, the procedure, and the precautions which must be taken in its interpretation.

PHYSIOLOGICAL BASIS OF THE TEST

It is now generally accepted by physiologists that, under certain conditions insulin indirectly stimulates both motor and secretory mechanisms in the stomach by way of the vagi. The impulses arise in the vagus center rather than in some part of the nerve itself, for complete transection of all vagal fibers passing to the stomach will prevent the usual gastric responses to this type of stimulation. It is not the insulin *per se* which stimulates the medulla but the hypoglycemia induced by the insulin injection. In most instances, unless the blood sugar be reduced to 50 mg./100 cc. or lower, no response will be evoked, regardless of the insulin dosage. Similarly, if the dosage of insulin is large enough to induce an adequate degree of hypoglycemia, but the latter is prevented by the administration of glucose or epinephrine, the muscular and secretory responses in the stomach will fail to occur—because of the absence of central stimulation. In diabetics with high fasting blood sugar levels, a single injection of insulin usually fails to cause a sufficiently low blood sugar concentration with the result that a gastric secretory response is not obtained. But, if injection of insulin is repeated, with the usual drop in blood sugar to levels

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²This study is part of a group project being carried on by Doctors Ralph Colp, Franklin Hollander, Percy Klingenstein, Vernon Weinstein, and Asher Winkelstein.

below 50 mg./100 cc., then a distinct rise in both volume and acidity of the gastric juice will occur. It has been suggested that vagal stimulation under the conditions of this test may be dependent on the rate of fall of the blood sugar concentration, rather than its absolute value. As yet there is no decisive evidence in regard to this point.

With these phenomena as a foundation, an insulin test was formulated some years ago (2, 4) for the differentiation of a vagal pouch from one which had been completely deprived of its parasympathetic innervation. The reliability of the procedure was established by a series of 29 experiments on 6 different dogs provided with Pavlov, Hollander-Jemerin, or Heidenhain pouches. In 2 of these animals, a vagal pouch was tested before and after it had been converted to a Heidenhain pouch, and in another case such conversion took place post-operatively by a spontaneous degeneration of the vagal fibers, probably at the isthmus between pouch and stomach proper. In all instances, without exception, the result of the test was in agreement with the anatomical designation of the pouch. On the basis of these experimental findings, a clinical test has been devised to determine whether any uncut abdominal branches of the vagus remain after bilateral vagotomy.

PROCEDURE

The test is at present a standard routine procedure in this Hospital for all cases in which a division or excision of the vagus nerve has been performed. For purposes connected with its evaluation, an insulin test has been done pre-operatively on every candidate for bilateral vagotomy or vagectomy. However, this is not essential for an evaluation of the operative procedure *per se*. The first postoperative test is being carried out 10-14 days following the operation. The test is being repeated at intervals of several months after the patient's discharge from the hospital, in the hope that such series of data may throw additional light on the physiological consequences of vagal interruption. The procedure is as follows:

(1) The patient is given a light (Sippy) diet the day before the test, with complete deprivation of food after 7 P.M., and fluid after midnight.

(2) As early as possible on the morning of the test, a 14 Fr. Levin tube is passed by mouth, omitting the usual sips of water. This tube must not be removed during the test period. The patient is instructed to expectorate all saliva.

(3) The fasting contents are aspirated completely with a 50 cc. Luer syringe, labeling the specimen "FC". Immediately thereafter, a sample of blood is drawn for the fasting glucose determination.

(4) Fifteen units of unmodified ("regular") insulin is injected intravenously

and the time of injection is recorded. Sterile glucose solution should always be available for intravenous administration if symptoms of severe hypoglycemia develop. The intravenous route was adopted for administration of the insulin because it had been employed by recent investigators (1, 3, 8). As yet, we have no systematic evidence to indicate that subcutaneous or other mode of administration is equally suitable, and until rigorous evidence on this point is adduced the intravenous procedure should be adhered to.

(5) Every 15 minutes after the injection, the stomach contents are completely aspirated, and a record made of the volume and time of collection, and of the presence of mucus and bile. A sample is kept for acidity titrations. Immediately following every second such aspiration except the last (i.e., every 30 minutes after the injection), a sample of venous blood is drawn for glucose determination. The aspirations are continued for 2 hours, thus giving 9 gastric samples including the "FC" specimen, and 4 blood samples including the fasting control. We have found that a single blood sugar value after the insulin injection, instead of 3 such values as specified here, is unreliable for our purposes. Of 79 insulin tests studied from this point of view, 55 (70%) showed a minimum blood sugar value at the end of 30 minutes and the remainder at the end of the second half-hour period.

(6) Analytical methods: Free and total acidities are determined on 0.5 cc. samples by the micro-titration technique generally employed in this Laboratory. This entails the use of buffer standards containing indicator for the precise determination of the end points: pH 3.5 with brom-phenol blue for free acidity, and pH 7.0 with phenol red for total acidity. Glucose is determined on whole blood by the Shaffer-Hartmann-Somogyi method, the specimens being mixed with sodium fluoride and thymol to prevent auto-glycolysis on standing as well as coagulation. For investigative purposes, all determinations are done in duplicate.

RESULTS OF THE TEST IN ULCER PATIENTS

The validity of this test procedure must rest not only on the animal experimentation but on the responses obtained with human subjects as well. The results with dogs, cited above, demonstrate (a) that vagally innervated gastric pouches, regardless of the extent of their parasympathetic innervation, invariably manifested a distinct rise in the free and total acidity curves of their secretion, associated with a fall in blood sugar to 50 mg./100 cc.; and (b) that pouches which were completely deprived of their vagal innervation never gave such a secretory response under these conditions. A series of insulin tests performed on patients, both before and after vagus section, revealed the following:

Patients without vagotomy. Up to the present, preoperative insulin tests have been performed on 43 patients with gastric or intestinal ulcer. Of these, 36 (84%) responded with a well-defined elevation in the curves for free and total acidities, and the remaining 7 (16%) with no rise whatever. In 5 instances, the discrepancy in the latter group could be traced to an inadequate depression of blood sugar, for when the test was repeated and an adequate hypoglycemia developed, a satisfactory secretory response was obtained. In both of the 2 remaining cases with a negative secretory response, the degree of hypoglycemia met the requirements of the test procedure. In one of them, however, a continuous gastric aspiration of the night secretion, performed 8 days before the insulin test, also failed to yield free hydrochloric acid. Hence, it seems likely that this patient presented at least a temporary failure of the glandular apparatus at the time the insulin test was done. In the second of these 2 cases with negative response, the minimum blood sugar value was 28 mg./100 cc. and the secretory curves were equivocal. This single instance of an unexplained negative response may be the consequence of a peculiarity in the rate of change of the blood sugar concentration. On the other hand, it may be a reflection of a phenomenon reported by Necheles (5), that gastric secretion and motility are both increased less (if at all) at very low blood sugar levels than at medium ones. Unfortunately, this patient left the hospital without operation before the test could be repeated. Hence, it may be concluded that the gastric acidity curve rose significantly in all but one of the cases which were tested according to the above procedure.

Patients with partial vagotomy. In a few cases, only a unilateral vagotomy (infra-diaphragmatic) was performed, sometimes combined with another gastric operation. All of these patients gave a positive secretory response to the insulin test postoperatively, indicating that some vagal fibers remained intact. These results are in accord with the observations on dogs, in which pouches of different degrees of vagal innervation were compared. They indicate that, unless there has been complete interruption of all vagal branches innervating the stomach, the insulin test may not be expected to yield a negative secretory response.

Patients with bilateral vagotomy. The results of the insulin test applied postoperatively to patients in this group are not as categorical as are those for the 2 preceding groups. Of 21 patients subjected to this operation, 11 (52%) gave a negative secretory response to insulin about 2 weeks following operation. In 2 of the latter, the blood sugar level did not fall below 50 mg./100 cc. and therefore the test is considered invalid. The results indicate that in at least 10 (48%) of this operated group, some of the branches of vagus nerve had not been interrupted. However, the percentage of cases with incomplete division of the vagi may be even greater than this, for some of the patients in whom a

negative response was obtained in the first postoperative test may give a positive one on subsequent repetition of the test—for reasons discussed in the following section.

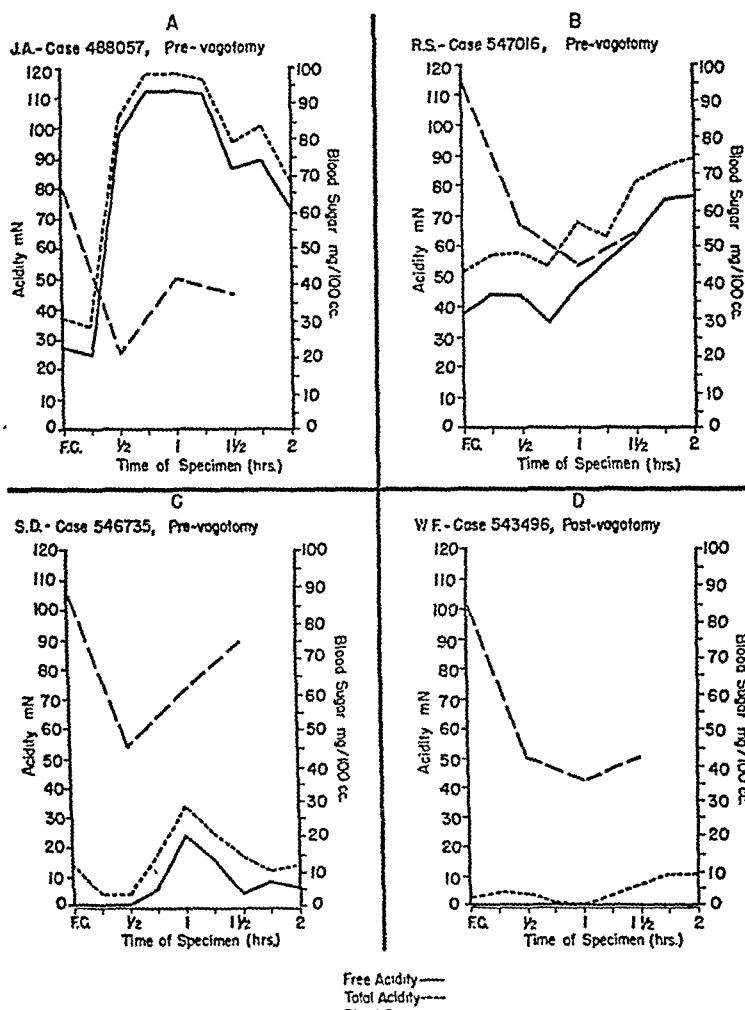


FIG. 1. GASTRIC ACIDITY AND BLOOD SUGAR CURVES ILLUSTRATING VARIOUS TYPES OF RESPONSE IN THE INSULIN TEST FOR THE PRESENCE OF UNCUT VAGAL FIBERS

CHARACTERISTICS OF THE ACIDITY CURVES AND PRECAUTIONS IN THEIR INTERPRETATION

In the presence of uncut vagus nerve, the curves for free and total acidity usually rise when the blood sugar level is depressed to 50 mg./100 cc. This

is designated as a *positive response*. The height of the curves, the duration of the elevated portion, and the latent period between the time of injection and the beginning of the rise all vary extensively, and they may depend on the acidity and rate of the fasting (pre-injection) secretion, the idiosyncrasies of the subject, the degree of hypoglycemia, and possibly even the rate of fall of the blood sugar level. The extent of these variations is well-illustrated by the data of A, B, and C in Figure 1. Because of this variability in the positive responses, the test is an indicator only of the presence or absence of intact vagal tissue, and not of the amount of nerve tissue which remains uncut. Hence, in patients with partial or unilateral vagotomies, no valid quantitative inferences can be drawn from the insulin test regarding the extent of vagal interruption which had been effected by the operation, and the test is of no particular value in such operations unless the possibility of degeneration of the remaining uncut fibers is under consideration.

On the other hand, what is the significance of a *negative secretory response*, characterized by the absence of a clear-cut rise in the free acidity curve following insulin injection? Such a response is far more equivocal than a positive one, since it may result from any one of several different conditions:

(1) First and foremost, all abdominal branches of the vagus, both primary and secondary, may have been transected so that no parasympathetic impulses reach the stomach.

(2) Even in the presence of some intact fibers, however, the secretory cells may not be stimulated because the neural impulses were never initiated centrally. This happens when the hypoglycemia fails to reach a sufficiently low level.

(3) A persistent depression of the free acidity curve may sometimes be encountered in the presence of both uncut vagi and a suitably low blood sugar. The subject may be completely and permanently achlorhydric, as demonstrated by the histamine test, and it is our practice to perform this test whenever uncertainty on this score exists. Even if there is no achlorhydria, however, the subject may suffer from a temporary inadequacy of the acid-secreting glands, necessitating a stronger stimulus than normal. This situation is sometimes encountered in the performance of an ordinary fractional analysis with a standard test-meal. There is no physiological explanation for this, except that it may be related to a postoperative gastritis. In such cases, repetition of the Rehfuss test after an interval of several days usually yields a positive secretory response—unless the anacidity be the result of a persistent fever, in which case the insulin test would probably not be performed anyway. For this reason all insulin tests which yield equivocal results are repeated routinely.

(4) Finally, the complete absence of free acidity, following insulin injection, may result from a positive response of low magnitude in which the hydrochloric

acid undergoes complete neutralization by regurgitated intestinal contents. This possibility arises particularly in patients upon whom a gastroenterostomy or a subtotal gastrectomy was performed, simultaneously with the vagotomy or previous to it. Such a reaction is suggested by a pair of curves which show no free acid throughout the entire 2 hours following injection, but a small elevation in total acidity correlated with the lowest blood sugar value. Acidity curves of this character are difficult to interpret. For instance, the results illustrated in fig. 1D may be the consequence of neutralization of a low acid output, or they may indicate the complete absence of a secretory response—for any one of the several reasons already stated. When a neutralization effect is suspected, and the alcohol Rehfuss test has demonstrated the absence of an anacidity, it is necessary to repeat the insulin test. This should be performed with an increased dosage of insulin, in an effort to augment the acid output and thus overcome the complete neutralizing action of the regurgitated intestinal contents. The persistence of a negative response, especially if the volumes of the gastric samples are small, enhances the likelihood that all of the vagal fibers had been interrupted.

SUMMARY

The foregoing report contains a detailed description of a physiological test for the presence of uncut vagus nerve fibers in ulcer patients, following any operation designed to interrupt all vagal stimuli to the stomach. The clinical success or failure of such operations is not discussed in this report. The test is based on the production of a degree of hypoglycemia of 50 mg./100 cc. or lower. To produce such a hypoglycemia, 15 units of insulin is administered intravenously; its production must always be proved by a series of blood sugar determinations. A fractional gastric analysis is performed to determine whether the resulting vagal stimuli, set up centrally, are able to evoke any secretory response from the stomach. The validity of this procedure for the purpose stated is supported by evidence derived from studies on gastric pouch dogs and on patients.

A positive response to the insulin test—consisting of a distinct rise in the curve for free acidity of the gastric aspirates, accompanying the production of an adequate hypoglycemia—indicates that some uncut parasympathetic fibers still connect the vagus center in the medulla with the stomach. This acidity curve affords no indication of the proportion of such fibers which remain intact; reasons for the qualitative character of the test are discussed. A negative response is suggestive but not necessarily conclusive proof that all the vagal fibers which pass to the stomach have been interrupted. First of all, there must be no doubt that an adequate hypoglycemia had been attained, and that neither a permanent nor a temporary anacidity was present—as shown by a

fractional analysis with a suitable test-meal. Secondly, in the presence of a gastroenterostomy or a subtotal resection of the stomach, the intestinal regurgitation may neutralize a small acid output and thus mask a true positive response. Such an equivocal result can often be resolved by a repetition of the insulin test—especially if the dosage of insulin be increased somewhat. Only after these possibilities have been eliminated can a negative response be interpreted to indicate the presence of no uncut vagal fibers.

REFERENCES

1. BABKIN, B. P.: Am. J. Dig. Dis., 5: 467, 1930.
2. HOLLANDER, F., JEMERIN, E. E., AND WEINSTEIN, V. A.: Federation Proc., 1 (Pt. II): 116, 1942.
3. IHRE, B. J. E.: Human Gastric Secretion. Oxford University Press, 1939.
4. JEMERIN, E. E., HOLLANDER, F., AND WEINSTEIN, V. A.: Gastroenterology, 1: 500, 1943.
5. NECHELES, H., OLSON, W. H., AND SCRUGGS, W.: Federation Proc., 1: (Pt. II) 62, 1942.
6. THORNTON, T. F., STORER, E. H., AND DRAGSTEDT, L. R.: J. A. M. A., 130: 764, 1946.
7. WEINSTEIN, V. A., COLP, R., HOLLANDER, F., AND JEMERIN, E. E.: Surg., Gynec. and Obst., 79: 297, 1944.
8. WELIN, G. AND FRISK, A. R.: Acta Med. Scand., 90: 543, 1936.

DISCUSSION ON SYMPOSIUM ON PEPTIC ULCER WITH PARTICULAR REFERENCE TO VAGOTOMY

PAPERS BY DRs. KEITH S. GRIMSON AND JULIAN M. RUFFIN, DURHAM, N. C.; AND DR. FRANKLIN HOLLANDER, NEW YORK CITY

DR. ASHER WINKELSTEIN (New York City): My colleagues and I have studied the pathological physiology of gastric secretion in peptic ulcer for 25 years. Our conclusion from nocturnal secretion curves, from sham feeding, and, recently, from the hypoglycemic effects of intravenous injections of insulin, is that the hyperchlorhydria and hypersecretion of peptic ulcer, when present, is mediated through the vagus nerves.

This seems to lay a firm basis for vagotomy in the therapy of peptic ulcer. However, it should be emphasized that one must exercise considerable caution in the interpretation of any new treatment for ulcer because 75 per cent of persons with uncomplicated ulcer go through life with mild symptoms and will improve temporarily, at least, with almost any form of medical therapy. This group, therefore, does not require surgical therapy. Twenty-five per cent of ulcers, however, are refractory and many of the patients do require surgical therapy.

We favor as the operation of choice in these cases subtotal gastrectomy since it removes the ulcer, removes the gastritis, gives an optimum motor result, and prevents recurrences in a large measure by establishing a harmless chronic achlorhydria in practically 100% of gastric angle ulcers and in 55 per cent of duodenal ulcers. We feel strongly that the only surgical therapy which will give a permanent cure for duodenal ulcer is an operation which is followed by a chronic, harmless achlorhydria.

Recurrences do occur after subtotal gastrectomy for duodenal ulcer in patients who after operation have free acidity with the usual test meals. This persistent acidity appears to be due to the vagus nerves since it is inhibited by atropine and the second or chemical phase has been eliminated by the removal of the antral tissue.

The idea of vagotomy arose logically for this group and anterior subphrenic section of one vagus was added to subtotal gastrectomy. The cases so treated were reported by Eugene Klein, A. A. Berg and myself before this Society (parenthetically for the first time in 1928!). Although the results seemed good, we have been unable to answer the criticism that the high percentage of achlorhydrias obtained (76 per cent) might not have resulted from the subtotal gastrectomy alone. As yet we do not know of any successful method for testing the effect of unilateral or partial vagotomy.

Because of this criticism, Dr. Ralph Colp in 1939 decided to perform complete, transthoracic, supradiaphragmatic, bilateral vagotomy in the therapy of recurrent jejunal ulcer after subtotal gastrectomy.

Since then, Dr. Lester Dragstedt instituted bilateral suprathoracic vagotomy alone as a surgical therapy for peptic ulcer. While this approach seems rational, and, if time proves it successful, will tend to demonstrate that peptic ulcer is a disease related to the vagus nerves, certain theoretical and practical considerations arise for discussion, viz.: (1) it is doubtful if all peptic ulcers are vagal in origin; (2) the vagotomy leaves a moderate amount of free acid due to the chemical (antral) phase, and this, plus sympathetic nerve influences, may cause a recurrence of the ulcer disease in the individual, (3) the severe gastric atony after complete vagotomy apparently necessitates gastro-enterostomy in approximately 20 per cent of the cases, and (4) the abolition of the parasympathetic innervation of the pancreas, biliary tract, kidneys and small intestines may ultimately lead to harmful effects.

Because of these objections, we still adhere to the idea that subtotal gastrectomy, especially when followed by an achlorhydria is a superior procedure. As we have pointed out repeatedly, the logic of the situation in duodenal ulcer where the persistent post-operative acidity is due to the vagus nerves, calls for the addition of bilateral *subphrenic* vagotomy to the subtotal gastrectomy in order to obtain a post-operative achlorhydria, or at least, an extreme sub-acidity.

Also, it has seemed preferable to us to use supradiaphragmatic, bilateral vagotomy in the therapy of recurrent jejunal ulcer after subtotal gastrectomy since the secondary abdominal operations for this condition are often complicated and may entail a high mortality.

Dr. Colp and his associate, Dr. Klingenstein, have carried out the operation of subtotal gastrectomy plus bilateral *subphrenic* vagotomy in a series of patients with duodenal ulcer. They have also performed a transthoracic bilateral vagotomy for severe recurrent jejunal ulcers after subtotal gastrectomy.¹

Although we realize that the series of cases is a recent one, we are nevertheless presenting it in order to stimulate some discussion concerning the relative merits of this combined approach as compared with simple supradiaphragmatic vagotomy alone.

The period of study is too short to permit conclusions from this series of cases. However, the impressions gained from this preliminary survey are: (1) that the combination of subtotal gastrectomy and subphrenic vagotomy is a logical one in the surgical therapy of duodenal ulcer, (2) that supradia-

¹ The details and results of these operations will be published later by Doctors Colp, Klingenstein, Hollander, Weinstein and the author.

phragnostic vagotomy should be studied as a substitute for secondary abdominal operations in the therapy of the severe recurrent jejunal ulcers, (3) that the effects on the post-operative acidity and clinical course seem good in the majority of our cases, and finally, (4) that it seems worthwhile to study carefully the indications for this combined approach and for the question of the use of bilateral vagotomy alone.

DR. CHESTER M. JONES (Boston, Mass.): I am reporting in a sense what Dr. Palmer did on the basis of work done by Dr. Moore, who started the supradiaphragmatic section of the vagus a little over two years ago.

We have operated on thirty patients, one-third with jejunal ulcers, and two-thirds with duodenal ulcers. All of them had intractable ulcers. In none of the cases was there obstruction. There were no gastric ulcers; in other words, we selected our group. All of the ulcers healed, even the largest and most outstanding jejunal ulcers.

I think the shortest time of healing, by x-ray, was ten days. There have been no recurrences of ulcer symptoms in any of the cases, over a period now of from one month to a little over two years.

Dr. Ruffin mentioned two patients who had symptoms after vagal resection. We also have had two. In a sense they were typical psychoneurotics who had ulcer symptoms, and the neurotic, or psychoneurotic symptoms remained but there are no ulcer symptoms present.

We have made use of the insulin test, which seems to me of extreme importance in establishing the integrity or section of vagal fibres in all of the cases, and have done that repeatedly since the patients were operated upon and so far there has been no evidence by that test of regeneration of vagus nerves. It seems to me that is one of the things we have got to follow very carefully.

One patient died six months after operation, from a cerebral vascular accident, and autopsy showed absolutely no regeneration that could be demonstrated, of the resected nerves.

There are unpleasant results but I think primarily they are immediately postoperative. We had one acute dilatation of the stomach which lasted five days, which subsequently returned to normal, and we have had one patient only in whom there was obstruction, and that patient has had a subsequent operation. I am sure that the suggestion that possibly a quarter of the patients or more need subsequent surgery for obstruction in selected cases is altogether too high.

Three patients had troublesome bowel symptoms such as Dr. Ruffin referred to, but they did not last more than two or three months.

I will mention one other case who had an ulcer and also had gastritis, which was demonstrated by gastroscopy. Post-vagotomy gastroscopy showed

disappearance of the signs of gastritis, and subsequently a moderate recurrence of the gastroscopic evidence, but no symptoms.

It seems to me this is still an experimental procedure. It is one of the most physiological approaches to the surgical control of ulcer that has been made, but all previous surgical maneuvers have had to undergo a period of test, and I am sure this must. Certainly another year or so is needed before the results can be properly evaluated. The results are immediately very dramatic. Whether they are due to motor changes, or secretory, or both, has still to be determined, but I am sure those two components can be studied over long enough period of time to evaluate properly the procedure.

DR. SARA M. JORDAN (Boston, Mass.): Last December when I accepted the invitation to discuss this symposium, I thought possibly at the Clinic we would have a large or a moderate group of cases which might lend some value to the discussion. We have, however, only one case in which supradiaphragmatic vagotomy has been done, the results of which parallel those which have been described this morning. I still think, however, that it may be well for me to use the time that has been allotted to me because possibly I may express some of the questions or doubts which have arisen in your minds, as this new approach to the treatment of ulcer has been discussed before an audience which I am sure is discriminating, skeptical, and at the same time eager for a new method of treating the intractable ulcer.

The things that came to my mind as I listened to this discussion were several: First of all, the reduction in acidity. How permanent will be it? Secondly, the reduction of motility. How advantageous is that? Dr. Grimson considers it of advantage to the patient.

As I look at these x-rays and perhaps ascribe the symptom of fullness in the upper abdomen to this condition, and possibly other symptoms which may follow later in the follow-up of these patients, I wonder whether the decrease in motility is advantageous or disadvantageous.

I should like also to ask Dr. Grimson, in the case in which the motility was restored to normal, whether the acid was likewise restored; in other words, do they go together? Secondly, it seems to me we must decide and prove whether or not the infradiaphragmatic vagotomy is less valuable than the supradiaphragmatic vagotomy. Since the surgeons who are to do various procedures must combine this, possibly, with other procedures, they should know what the difference in the results of these two operations is.

To me, who has a very definite prejudice against gastro-enterostomy and pyloroplasty, it seems that the combination of supradiaphragmatic vagotomy and one of those operations is undesirable. That may be purely prejudice.

The use of supradiaphragmatic vagotomy alone in cases of intractable duodenal ulcer seems strikingly good. It will be interesting perhaps two years from now to have another discussion of this same subject and see whether the test period proves that this operation is as valuable as it appears striking at the present time.

DR. WALTER L. PALMER (Chicago, Ill.): I should like to limit these remarks, if I may, to the subject of the pain mechanism in peptic ulcer.

We had one patient who continued to have pain after vagotomy. Dr. Dragstedt's associate, Dr. Storer, has carried out the acid test in a patient with a very sensitive duodenal ulcer, and he was able to produce pain after vagotomy as well as before vagotomy, in contrast to the experience of Dr. Grimson. This and other evidence suggests that the pain is mediated by way of the sympathetic rather than over the vagi.

Ulcer pain is dependent upon a lowering of the pain threshold of the nerves to the stomach. We all know that these nerves are ordinarily insensitive, and something happens to them in the ulcer process to lower the threshold so that they are stimulated by acid, or they are stimulated by pressure, or by peristaltic waves. I think we do not know exactly what it is that lowers this pain threshold, but it seems to be related to the inflammation which we conceive to be a chemical type of inflammation.

This pain mechanism can fluctuate very rapidly from a sensitivity to peristaltic waves over to a sensitivity to acid or insensitivity.

If I try to explain the observations of Dr. Grimson and Dr. Ruffin with regard to the subject of insensitivity, I find it rather easy to do so in the duodenal ulcers, and in the jejunal ulcers, primarily because of the decreased motility. Now, that doesn't mean that I think the motility is responsible for the pain, but rather that with duodenal and jejunal lesions, decreased motility means decreased emptying, and that means the rate at which the acid comes in contact with the ulcer is markedly diminished.

One can take a very sensitive duodenal ulcer and if for some reason the acid does not leave the stomach, pain will not be produced, but when the acid does leave the stomach, pain then ensues.

This explanation would account for the cases mentioned by Dr. Ruffin, with the exception of the last one, in which they had a very sensitive gastric ulcer and apparently were able to produce pain with acid, and a few hours after vagotomy were not able to induce pain with acid. I do not know what the mechanism is, but I think it is not related to muscle tension.

DR. FRANK H. LAHEY: May I ask a question while we have Dr. Palmer here? Have you any figures or even any impression as to the efficacy of supradiaphragmatic vagotomy vs. infradiaphragmatic vagotomy?

DR. PALMER: We have no figures, but I am glad you asked the question because it gives me an opportunity to say in the more recent cases in which Dr. Dragstedt has combined gastro-enterostomy and vagotomy, he has performed a supradiaphragmatic vagotomy by a transabdominal approach, pulling down the lower end of the esophagus and cutting the vagi in the abdomen, but at the suprathoracic level.

DR. SIDNEY PORTIS (Chicago, Ill.): In the short time allotted to me, it is too difficult to discuss the philosophical approach of this operative procedure. I should like to report, however, some of our operations, particularly on one patient, in a series of three, and then discuss with you for just a moment what our reaction is to this problem.

In the first place, I want to sound a note of warning that when you relieve the ulcer patient of his pain, in some of these deep-seated psychoneurotic patients you may be dumping that patient into a severe depression; however, if I were put in a position of deciding whether I wanted to have repeated hemorrhage or perforation, or a depression, I think I would take the depression rather than the results or the complications from an untreated ulcer.

This particular patient that we are reporting is a sixty-five-year-old man who had had his ulcer symptoms for a period of over twenty years, with repeated hemorrhages, and I suggested to the men on my ward that we do a supradia-phragmatic vagotomy. Previous to operation he had a flat glucose tolerance curve. Following the giving of 1/150 grain of atropine it returned to normal, and following supradia-phragmatic vagotomy it was also normal.

I reported about two years ago that I thought the early morning pains of peptic ulcer were related to relative hypoglycemia which the patient developed at that time.

After operation the patient developed 100 per cent retention at six hours, and he had a great deal of distress. It was I who had advocated the operation and nobody is so hypercritical as residents and interns, and they came at me en masse and said, "What are you going to do now? This patient is a poor surgical risk." I had to use ingenuity and get out of that spot, so I decided to try some prostigmine. We gave 15 mg. of prostigmine three times a day. The patient was able to eat with comfort and began to gain in weight following this. Following an injection of 1 to 2000 prostigmine, a stomach which did not empty at the end of six hours now emptied at the end of four hours, and so I suggest to those of you who are so surgically-minded, in treating this gastric retention that you first try out prostigmine on your patients.

DR. S. A. KOMAROV (Philadelphia, Pa.): Within the past year Dr. Shay and I observed the immediate and remote effects of vagotomy (bilateral and

unilateral) on gastric secretion, motility and nutrition in 142 rats. The work was facilitated greatly by the favorable anatomical relations in the rat which permit complete severance below the diaphragm of all vagus branches to the stomach with ease and a minimum of operative trauma. It has been established that rats have a pronounced interdigestive phase of gastric secretion. We found in acute experiments that bilateral vagotomy virtually abolished the interdigestive phase in unanesthetized rats in the same manner as did full doses of atropine (0.25 gm. per kg. body weight, or more). Unilateral vagotomy approximately halved the rate of secretion without affecting acidity, total chloride or pepsin.

Experiments on chronic vagotomized rats demonstrated that the secretion remained reduced to very low values for as long as 14 weeks, and sham feeding in animals with gastric fistula, esophagotomy and pylorus ligated failed to produce any gastric secretory response. In control animals (same diet) with vagi intact sham feeding evoked a strong secretion. Thus the vagi are the secretory nerves for the stomach in the rat, as they are in man, dog and cat. Our data also show that the stimuli responsible for interdigestive secretion in the rat are transmitted through vagi. This fact combined with the high susceptibility of the rat to gastric ulceration (as contrasted to high resistance of dogs and cats) makes the rat very useful for the study of the relation of vagotomy to peptic ulcers. Our observations of the effects of bilateral vagotomy other than those on secretion seem to be of considerable interest.

The most striking effects of a successful bilateral vagotomy were on the condition and survival time of the animals. They stood the surgery well. After 24 hours they took milk eagerly and on the third day postoperatively ate any other diet offered to them. Appetite was excellent; *they ate voraciously*. However, when placed on our stock diet in another day or two they stopped eating and within two or three days more they usually died. None lived more than 10 days. At postmortem examination the wound was well healed and no abdominal adhesions were found. The stomach was very large and filled with tightly packed food; food was present in the dilated esophagus and at times also in the mouth cavity and even in the nostrils. Obviously, inadequate digestion and motility were responsible for the early death of these animals.

Since choline was shown by us to be an effective gastric secretagogue for the rat and because of its well known effects on motility, we added choline (70–150 mgs. per day) to the diet. Animals so treated lived considerably longer (up to one month) but failed to gain weight. Such large doses of choline proved to be toxic. Only when placed on diets in which proteins were replaced by peptones did the vagotomized rats survive as long as four months and gain weight although in a rather irregular manner. In these animals the inadequacy of motility caused by vagotomy also could be demonstrated in a very striking

manner. Motility was adequate for the propulsion of fluids but not for solids. Every two to four weeks the stomach developed tightly packed hair balls (2-4 cc. in volume) which had to be removed surgically to enable the animals to survive.

The discussed changes in motility are demonstrated by the slides, showing the dimensions of the stomachs and their contents in a normal animal (control) on the house diet and on three doubly vagotomized animals on house diet, on house diet plus choline and on peptone diet. The animals were starved on the ninth day after vagotomy and sacrificed 24 hours later.

In general our data on the various effects of bilateral vagotomy in rats are in agreement with the results obtained by Pavlov and co-workers on vagotomized dogs. In several papers and dissertations published from Pavlov's laboratories during the last decade of the past century (which unfortunately are available in Russian only) it was emphasized repeatedly that complete vagotomy eliminates a number of vital visceral functions. Bilateral vagotomy according to Pavlov interferes especially with gastric and pancreatic secretion, with gastric motility, with digestion and nutrition in general. It converts a normal healthy animal into an "invalid" organism which inevitably dies unless managed very carefully. Only with the most meticulous care did Pavlov and his associates keep a few vagotomized dogs alive for 9 months or longer. It was very difficult to maintain the normal weight in these dogs. The cause of death in their vagotomized dogs (barring accidents) was always inadequate digestion.

Our results as well as Pavlov's indicate that bilateral vagotomy interferes seriously with a number of essential visceral functions and from a physiological standpoint must be regarded as a grave operation.

From the results in animal experiments it is obvious that patients in whom bilateral vagotomy is performed should be watched carefully for late effects of this operation.

DR. HEINRICH NECHELES (Chicago, Ill.): Maybe another physiologist should say a few words. We will have to wait for many years to know the trophic effects of section of the vagi on such organs as the pancreas, the liver, the intestinal mucosa, and so forth, and we therefore have to wait for late results of this operation in man and in animals. I partook in a discussion with Dr. Ivy about ten years ago. We could not confirm the large volumes of secretion found by Dr. Dragstedt in dogs with pouches of the whole stomach with vagi intact, and Dr. Ivy expressed the belief that it is probably traction on the vagi which produced this hypersecretion.

Vagotomy in dogs often produces ulcers of the stomach, particularly when these dogs get rough food and are exposed to cold. We should keep that in

mind, too. The free acidity following vagotomy is decreased, but this may be an apparent and not a true reduction because, when gastric juice is collected over night at room temperature and then is titrated, much or all of the free acid has been bound, the degree of neutralization depending on the content in mucus, saliva, duodenal juice, and so forth, of the gastric juice. Depending on the amount of such neutralizing factors, the gastric juice of one person may lose its free acid faster than that of another person. You know, when you keep a sample of acid gastric juice an hour or two at room temperature the red color of Toepfer's reagent disappears, and I think this may have occurred in the tests we just have heard about, because combined and total acidity did not change much following vagotomy.

Concerning the effect of vagotomy on acid secretion; we have evidence that the increased acid secretion in animals with ulcers is due to the local lesion; in the Mann-Williamson dog, for example, acidity does not go up until an ulcer is formed, and I believe that the increased acidity is due to a local reflex in the stomach. Vagotomy may abolish the motor disturbance of the local lesion in the stomach.

Concerning the insulin test, I should like to say that it may be misleading, for, if the blood sugar drops to too low levels or drops too fast, other mechanisms come into play which abolish the stimulating effect, and we have reported that there may be an actual inhibition of acid secretion.

DR. KEITH S. GRIMSON (Durham, N. C.): The interest in this study of vagotomy for peptic ulcer and the critical discussion is appreciated. Indications for the use of transthoracic vagotomy alone or for subdiaphragmatic vagotomy with gastroenterostomy or subtotal gastric resection can not be determined at present. Our early results suggest that transthoracic vagotomy may be used alone in certain patients or with gastroenterostomy in others, even though retention or diarrhea may cause some difficulty. Resection with vagotomy may add complications unnecessarily. Secondary vagotomy for recurrence after resection may be better justified.

Doctor Jordan asked about the permanence of the reduction of acidity and motility. Reduction of acidity has been variable but there has as yet been no definite tendency toward recovery. Motility, as judged by balloon studies, remained markedly reduced except for one patient who, after eighteen months, exhibited low waves about equal to those present before operation. Values for free acid at this time were slightly lower than in the early post-operative period.

Doctor Portis described decrease of retention after Prostigmine. Prostigmine, Mecholyl, Doryl and other drugs have produced either no response or

an equivocal one after vagotomy as judged by our balloon studies. Note: Recent observations of Machella, Hodges, and Lorber that Urethane of B-Methyl Choline is effective have been confirmed.

We certainly agree that vagotomized experimental animals tolerate food poorly and often do not have changes of gastric motility or secretion parallel to those observed in patients.

Vagotomy at present remains a problem for careful clinical investigation. Additional information concerning complications and late effects will be necessary before it can be properly evaluated.

THE EFFECTIVENESS OF PARENTERALLY ADMINISTERED "ENTEROGASTRONE" IN THE PROPHYLAXIS OF RE- CURRENCES OF EXPERIMENTAL AND CLINICAL PEPTIC ULCER¹

WITH A SUMMARY OF 58 CASES

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This communication represents the synthesis of a series of investigations on enterogastrone, all of which were designed for the purpose of appraising its utility in the treatment of peptic ulcer as encountered clinically in man. The objectives of previous studies have been (a) the evolution of a method of preparation of a suitable concentrate of the chalone to give a product of uniform potency and of reasonable biological purity, non-toxic and injectable in the human; (b) a thorough examination of its efficacy in preventing the development of post-operative ulcers in a series of dogs prepared by the Mann-Williamson operation; and (c) a clinical trial on patients with proven peptic ulcer, entailing a series of sufficient size, observed over a period of time of adequate duration, in order that a warrantable evaluation of the therapy might be possible.

In a series of earlier reports we have indicated the processes involved in the preparation of the enterogastrone concentrate used (1, 2), the protection afforded Mann-Williamson dogs by the parenteral injection of such concentrates (3, 4, 5), and a preliminary survey of a small series of patients (5). It was noted that a concentrate which was potent in repressing the secretory activity of the parietal cells manifested an unequivocal protective effect in the Mann-Williamson dog, outlasting the duration of the injections; and that the results of preliminary observations on patients suffering from peptic ulcer were sufficiently favorable to indicate an amplification of the therapeutic trial of the material. The present contribution deals with the current status of this investigation.

METHODS

A. *Preparation of the enterogastrone concentrate.* Although the various stages in the production of this material have been described in previous reports (1 2), it is believed that a summary of the complete process, with minor modifications since introduced, is pertinent. The source material employed is the

¹This work was aided in part by a grant from the Abbott Laboratories.

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first six to eight feet of small intestine from freshly slaughtered hogs. The strips of intestine are everted at the abattoir, washed with water, and suspended in cold 0.4 per cent HCl with occasional stirring, in the proportion of eighty liters to four hundred intestinal strips. At the end of thirty minutes the intestines are removed and wrung out by hand into the acid extract, which is then strained through cheesecloth and shaken vigorously with sufficient dry NaCl to saturate it, or about 30 per cent of the weight of the acid extract. The resulting suspension is brought back to the laboratory and the precipitate is collected by filtration to the consistency of a stiff paste which has a total solid content of about 35 to 40 per cent. This product, designated "A-precipitate," has in our experience served as a highly satisfactory source of all the gastrointestinal hormones. Uniformly potent enterogastrone concentrates are obtainable from this product stored under refrigeration for up to two to three months. About eight kilos are obtainable from 400 intestinal strips.

Purification is effected by suspending three kilos of A-precipitate in thirty liters of water with the aid of a Waring blender, adjusting the suspension to its isoelectric point, pH 5.4, by the addition of NaOH solution, bringing the adjusted mixture to a boil with a current of live steam, and filtering off the precipitated and coagulated inert material. The clear filtrate is cooled with running water and treated with a saturated solution of pure (resin-free) tannic acid to the point of complete precipitation, in the proportion of about 100 cc. to 4 liters of chilled filtrate, and the resulting precipitate centrifuged out, washed by suspension with distilled water, 5 per cent acetic acid, and finally with water. It is then triturated thoroughly with 70 per cent aqueous acetone containing 2 per cent of its volume of concentrated HCl, the suspension centrifuged vigorously, and the supernatant fluid filtered into 8 to 10 volumes of pure dry acetone. The insoluble, inert residue is washed with acidified acetone and the washings are combined with the first extract. Throughout the manipulation of the tannic acid precipitate the temperature must be low and the centrifugings brief in order to avoid a gummy product which is difficult to handle, and the entire process must be continuous without pause.

The abundant colorless amorphous precipitate resulting from the flooding of the acid-acetone extract with acetone is allowed to settle, the supernatant fluid siphoned off and discarded, and the precipitate centrifuged out and washed twice with absolute methanol containing 1 per cent of its volume of concentrated HCl, and finally with acetone. The acetone-wet precipitate is dissolved in a large volume of cold distilled water; for the yield from 3 kilos of A-precipitate (amounting to about 60 grams in dry weight) 15 liters of water is used. To this solution is added a saturated solution of picric acid in warm acetone to the point of complete precipitation; the above-mentioned amount requires approximately 150 grams of picric acid. The resulting precipitate is

centrifuged out, packed tightly in the cups, and then is triturated with the same acid-acetone mixture employed to decompose the tannate, using a Waring blender to consummate a thorough mixing. The resulting suspension is centrifuged long and hard, the supernatant fluid decanted into an excess of acetone, and the residue washed with acid acetone and the washings added to the first extract. The residue is discarded. The white amorphous material precipitated by the acetone treatment is centrifuged out, washed repeatedly with acetone until all traces of picric acid are removed, and finally with a 1:1 mixture of acetone and dry ether and finally ether, and is dried in vacuo. Approximately 30 grams are obtained from 3 kilos of A-precipitate. The product is colorless, easily soluble in water, and possesses a unitage of 25 milligrams in repressing histamine-induced gastric secretion in the total pouch dog (1). It has little if any inhibitory action on gastric motility, in contradistinction to the cruder product prior to the picric acid treatment. Tests on a series of guinea-pigs have revealed it to be entirely non-antigenic.

For purposes of injection, the material is dissolved in boiling sterile water in a concentration of 50 milligrams per cc. and stored in sterile rubber-capped bottles. Occasional tests have revealed such solutions to remain sterile and potent up to 10 days after bottling; periods of storage of longer duration have not been tested. Two pharmaceutical houses have ampouled our material in the lyophilized state, a form which has transpired to be highly satisfactory.

B. *Animal experiments.* Dogs prepared by the Mann-Williamson operation, totalling 43 in number, served as experimental material. The details of their preparation, care, and feeding are described in a preceding article (3). They included a series of 25 dogs given injections of 100 milligrams of the cruder tannic acid product twice daily intravenously; a group of 10 which served as controls, receiving in the same amount and dosage a similarly prepared extract from pork muscle, to exclude any possible non-specific effects; and, finally 8 dogs which were given a single daily intramuscular injection of the more highly purified concentrate. Injections were made every day for a period of a year, and the animals were observed continuously during treatment and after its cessation. In no case were any other anti-ulcer measures applied at any time. Animals dying during the course of observation were routinely autopsied, to determine whether the fatality occurred on the basis of an ulcer.

C. *Therapeutic trial in peptic ulcer in man.* A considerable amount of care has been exercised in the selection of the patients comprising this experimental series. In order to establish the value of this form of treatment in the face of the technical difficulties involved in securing adequate amounts of enterogastrone, the procedure of choice was to use each patient as his own control, in other words, to compare the number of acute exacerbations prior to the inception of treatment with those occurring during the course of injections and

after their cessation. To make such a plan effective, the patients investigated were limited to those who had a history of peptic ulcer dating back five years or more, and who could provide reasonably accurate information regarding the frequency, nature, and severity of previous attacks. In addition, it was necessary to enlist their cooperation in continuing to report for injections for the specified length of time, irrespective of whether they felt no benefit on the one hand, or whether they felt so markedly improved that no further treatment was required on the other hand. The cases detailed below include only those who conformed to such a schedule. In all cases our diagnostic study confirmed that made by several internists whom the patients had consulted during previous years for diagnosis and treatment of recurrences.

At the inception of treatment the patients were allowed to remain on any current form of management, or were given conventional antacid therapy in the form of Al(OH)_3 or AlPO_4 if in marked distress. The solution was injected intragluteally under aseptic precautions, using a 5 cc. Luer syringe and a No. 24 needle of $\frac{3}{4}$ to 1 inch length, in a dosage of 100 milligrams for the first few injections, after which 200 milligrams were given throughout the course of treatment. Any particular diet which had been established at the outset of therapy was maintained until relief of distress was reported, after which the diet was liberalized until a regimen of three meals a day, excluding irritating food and beverages, was attained; at this point, varying in the individuals in the series, other forms of management were likewise discontinued. X-ray examination of the upper gastrointestinal tract was performed routinely at the outset of treatment, and at intervals of one to three months thereafter.

An impression of clinical improvement in these patients was based on the following criteria: 1) relief of acute symptoms, such as pain, distress, bleeding or vomiting, 2) gain in weight or similar evidences of betterment in general physical condition, and 3) the radiologist's reports regarding the appearance of the upper gastrointestinal tract during the course of injections. Any acute exacerbations occurring while treatment was in progress were dealt with by such direct methods of conventional therapy as were deemed appropriate. Injections of the enterogastrone concentrate were made three times a week in 32 patients, and daily excepting Sundays in the remaining 26. They were, or are being, continued for a year, with the exception of three patients in the daily injection series who were discontinued after six months. Following completion of the course of injections the condition of the patients was checked at intervals of 3 to 4 times a year.

RESULTS

A. *Effectiveness of enterogastrone against development of ulcers in the Mann-Williamson dog.* In previous reports we have indicated (3, 4, 5) the ability

of parenteral enterogastrone therapy to effectively prevent the development of ulcerative lesions in the experimental animal, and the exclusion of any possible non-specific effect as evidenced by the failure of pork muscle extract to exert

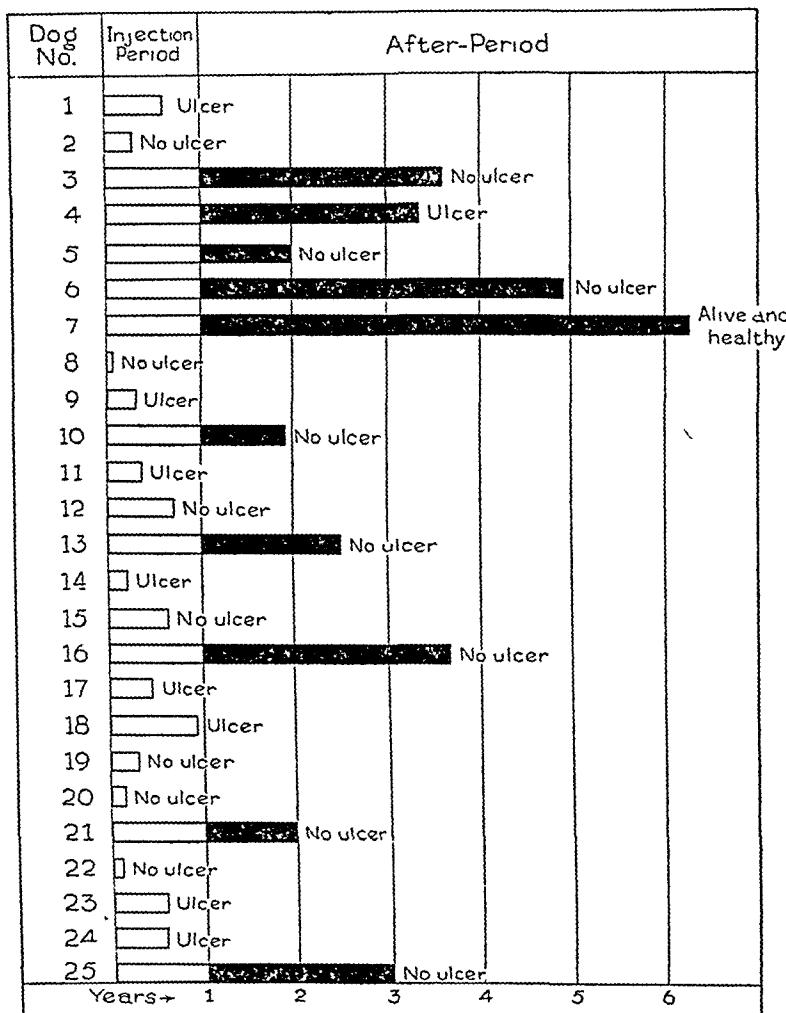


CHART I. LONGEVITY AND INCIDENCE OF ULCER IN 25 MANN-WILLIAMSON DOGS FROM DATE OF BEGINNING INJECTIONS OF 50 MILLIGRAMS OF CRUDE ENTEROGASTRONE CONCENTRATE THREE TIMES DAILY

any protective influence. The present status of the series of 43 animals is depicted in the charts, which reveal that among the first series of animals investigated, 15 of the 25 enterogastrone-treated dogs died within the 12-month injection period (Chart I); 8 of these animals died of ulcer, and 7 of

other causes. The remaining 10 dogs, survivors during the year's course of injections, were taken off injections at this time; the original intent in so doing was to permit an ulcer to develop and determine the efficacy of a resumption of the injections in producing healing. However, it was found impossible to carry out such a study as planned, owing to the unexpected failure of the animals to develop ulcers following a cessation of therapy; and the subsequent course of the dogs in this series has revealed the protective effect of entero-gastrone to endure long after completion of its intravenous administration daily over a period of a year. Of this group of 10 dogs, one is still living and in excellent condition, nearly 6 years after operation, the last 5 years of which have been devoid of any ulcer management. The remaining nine animals died at intervals ranging from 11 to 48 months after cessation of therapy; eight of these expired from miscellaneous causes, and were noted to be free of ulcer on autopsy; one dog succumbed to a perforated ulcer 28 months after treatment had been discontinued.

The ten dogs which were given control injections of pork muscle extract, designated 1C to 10C, all died of ulcer in an interval consistent with the expectancy in the untreated Mann-Williamsn animal (3) (Chart III). The remaining eight dogs (26 to 33) were treated with the more highly purified concentrate given intramuscularly in one daily 100 milligram dose; in other words, the form of therapy designed for employment in peptic ulcer in man. Three dogs of this series failed to weather the twelve-month period during which injections were made; one of these died with an ulcer, the other two deaths were due to extraneous causes. The five animals surviving the year of therapy transpired to have received the same lasting protection as occurred in the intravenous series. Three of them died of causes other than ulcer, 14 to 18 months after cessation of therapy; one is living and in excellent condition four years after operation, in the last three of which no ulcer management has been applied; and one died of a perforated ulcer after 2.5 years (Chart II).

B. *Application to peptic ulcer in the human.* Roentgenological examination at the inception of treatment revealed that 51 of the patients evidenced duodenal ulcers, 4 had post-operative jejunal lesions, 2 suffered from gastric as well as duodenal ulcers, and one had a gastric ulcer. Many of the patients reported symptomatic relief within a few days after the injections were begun; most of them were free of distress after two weeks; in the remaining few approximately two months elapsed before relief from pain and distress was complete. In most instances, an interval of two to five months was required before evidences of improvement were manifest on X-ray examination as interpreted by a trained radiologist. A summary of the status of the patients prior to therapy, and their response to treatment, is listed in Tables I and II. A detailed survey of the group studied is provided below.

Series I—Six injections per week. Included here are a total of 26 patients, all presenting a history of ulcer dating back from 5 to 47 years.

Case 1. S. K., male, a laborer, aged 58, was diagnosed as suffering from duodenal ulcer in 1933. Since that time he had experienced pain and distress almost con-

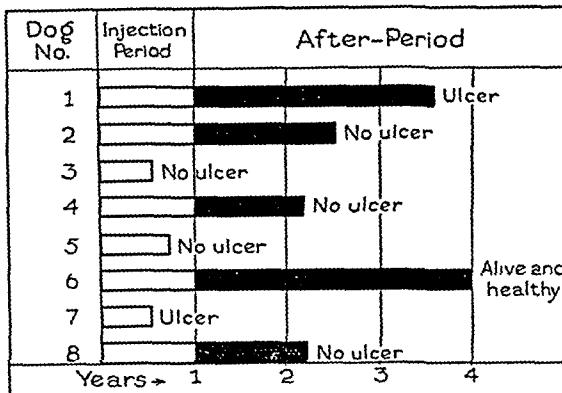


CHART II. LONGEVITY AND INCIDENCE OF ULCER IN 8 MANN-WILLIAMSON DOGS FROM DATE OF BEGINNING INJECTIONS OF 100 MILLIGRAMS OF PURIFIED ENTEROGASTRONE CONCENTRATE DAILY

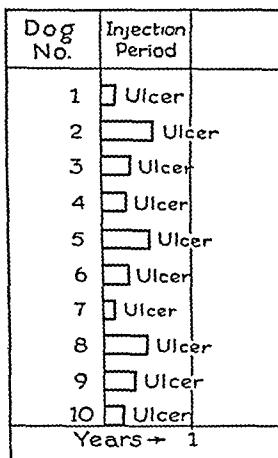


CHART III. LONGEVITY AND INCIDENCE OF ULCER IN 10 MANN-WILLIAMSON DOGS FROM DATE OF BEGINNING INJECTIONS OF 50 MILLIGRAMS OF HOG MUSCLE EXTRACT THREE TIMES DAILY

tinuously. On X-ray examination the duodenal bulb was noted to be irritable and deformed, in a configuration typical of duodenal ulcer. He was given daily intramuscular injections of enterogastrone, and reported symptomatic relief in four days. Injections were continued from September 1, 1943, to March 1, 1944, during which time he remained asymptomatic; in the 28 months elapsing since treatment was

TABLE I
Series I—6 injections per week

CASE NUMBER	PREVIOUS HISTORY							RESPONSE TO TREATMENT							Remarks
	Location	Years present	Number of attacks per year	Distress	Bleeding	Retention	Niche	Months on treatment	Symptomatic relief	X-Ray Improvement	Recurrences while on treatment	Months since stopping treatment	Recurrences after tr. stopped		
1	D	10	Many	Yes	No	No	No	6	Yes	Yes	0	28	0		
2	D	25	Many	Yes	No	No	Yes	12	Yes	Yes	0	6	0		
3	D	8	6 or more	Yes	Yes	No	Yes	12	Yes	Yes	0	5	0		Asymptomatic cholelithiasis; Penetrating ulcer when treatment was started
4	D	27	Many	Yes	No	No	Yes	12	Yes	Yes	0	3	0		
5	G & D	6	Many	Yes	No	No	Yes	12	Yes	Yes	0	3	0		
6	D	10	2	Yes	No	No	No	12	Yes	No	0	2	0		
7	D	18	Many	Yes	No	No	Yes	3 + 4	Yes	Yes	0				Penetrating ulcer. Stopped treatment at 3 months. Niche returned at 7 months. Treatment resumed. History of perforation and hemorrhage. Gastro-enterostomy 1 year ago without relief.
8	D	18	Many	Yes	Yes	No	Yes	11	Yes	Yes	0				
9	D	6	5-6	Yes	No	No	No	12	Yes	Yes	0				
10	D	8	2	Yes	No	No	Yes	12	Yes	Yes	0	4 less than 1	0		
11	D	5	Many	Yes	Yes	No	Yes	12	Yes	Yes	0	1	0		
12	G	6	2	Yes	No	No	No	6	Yes	Yes	0	4	0		
13	D	6	3-4	Yes	No	No	No	6	Yes	Yes	0	3	0		
14	D	47	Many	Yes	Yes	Yes	Yes	9	Yes	No	1				
15	D	6	2-3	Yes	Yes	No	Yes	8	Yes	Yes	0				Marked improvement after 1 month treatment.
16	D	10	Many	Yes	No	Yes	Yes	7	Yes	Yes	1				High-grade retention.
17	D	10	2 to 6	Yes	Yes	No	Yes	6	Yes	No	1, 4 mo.				Repeated hemorrhages before treatment. One on treatment. Complicating brucellosis.
18	D	12	Many	Yes	No	No	Yes	6	Yes	Yes	0				4 cm. niche at start of treatment. Filled at 6 months.
19	D	9	3 to 5	Yes	No	No	Yes	5	Yes	No	0				
20	J	7	Many	Yes	Yes	No	Yes	5	Yes	No	1, 3 mo.				
21	D	8	2 to 4	Yes	No	No	Yes	4	Yes	Yes	0				
22	D	15	2 to 4	Yes	No	Yes	Yes	8	Yes	Yes	0				

TABLE I—Continued

CASE NUMBER	PREVIOUS HISTORY							RESPONSE TO TREATMENT							Remarks
	Location	Years present	Number of attacks per year	Distress	Bleeding	Retention	Niche	Months on treatment	Symptomatic relief	X-Ray Improvement	Recurrences while on treatment	Months since stopping treatment	Recurrences after tr. stopped		
23	D	5	Many	Yes	No	Marked	?	3	Yes	?	0				High grade retention. Duodenum not visualizable.
24	D	10	2	Yes	No	No	Yes	4	Yes	Yes	0				
25	D	7	1	Yes	No	No	No	12	Yes	No	0				
26	D	6	3	Yes	No	No	No	9	Yes	No	0	7	0		

discontinued, his course was entirely uneventful. Improvement in the deformed appearance of the duodenal bulb has been apparent since completion of the course of treatment.

Case 2. B. K., female, a housewife, aged 53, was diagnosed as manifesting a duodenal ulcer in 1920, and since then had experienced continuous pain and distress of varying severity. X-ray examination revealed the presence of a deformity and pseudodiverticulum in the duodenal bulb, as well as an ulcer niche. In addition, a solitary calcified gall-stone was present, but cholecystographic studies showed the gall-bladder to concentrate and evacuate normally. Enterogastrone injections were begun on December 2, 1944, and continued six times weekly to the same date in 1945. Relief of symptoms was reported in 10 days, and the post-injection X-ray studies have shown only a residual deformity. She has been uninterruptedly free of distress.

Case 3. K. R., male, an engine-room laborer, aged 33, had experienced six or more acute exacerbations since 1936, at which time a diagnosis of duodenal ulcer had been established. Injections were begun on January 20, 1945, with the presence of occult blood in the stool, and X-ray evidence of a penetrating duodenal ulcer. Relief from acute symptoms in one week was reported by the patient; he has been entirely asymptomatic since four months after treatment was started, including its discontinuance on January 20, 1946. Roentgenological examinations made after therapy have revealed filling of the crater, and the presence of a residual deformity of the bulb.

Case 4. G. A., male, aged 59, an attorney for a large banking corporation was first diagnosed as suffering from duodenal ulcer in 1918. Since then he was under more or less continuous Sippy management, with constant pain and distress. Injections were begun on March 12, 1945, at which time X-ray studies revealed the presence of a duodenal deformity and crater typical of ulcer. Symptomatic relief was reported in three weeks, and disappearance of the crater in six months. Injections were discontinued after a year, and the patient has remained free of ulcer distress; during the course of observation he has on three occasions experienced

TABLE II
Series II—3 injections per week

CASE NUMBER	PREVIOUS HISTORY							RESPONSE TO TREATMENT							Remarks
	Location	Years present	Number of attacks per year	Distress	Bleeding	Retention	Niche	Months on treatment	Symptomatic relief	X-RAY Improvement	Recurrences while on treatment	Months since stopping treatment	Recurrences		
27	D	11	Many	Yes	No	No	Yes	12	Yes	Yes	0	27	0	Complete healing	
28	D	5	Many	Yes	No	Yes	Yes	12	Yes	Yes	0	27	0		
29	D	6	Many	No	No	No	No	12	Yes	Yes	0	26	0		
30	D	5	Many	No	No	No	No	12	Yes	Yes	0	23	0	Marked reduction in gastric acidity.	
31	D	13	Many	Yes	No	No	Yes	12	Yes	Yes	0	20	0		
32	D	5	Many	Yes	Yes	No	No	12	Yes	Yes	0	19	0		
33	D	7	Many	Yes	No	No	Yes	12	Yes	Yes	0	16	0		
34	D	15	2 to 4	Yes	No	No	Yes	12	Yes	Yes	0	16	?	No follow-up possible.	
35	D	8	Many	Yes	No	Yes	Yes	6	Yes	Yes	0	30	?	No follow-up possible.	
36	D	6	Many	Yes	No	No	No	12	Yes	Yes	0	14	0		
37	D	6	Many	Yes	No	No	No	12	Yes	Yes	0	11	0		
38	J	12	Many	Yes	Yes	No	No	12	Yes	Yes	0	9	0		
39	D	15	2	Yes	No	Yes	Yes	12	Yes	No	1	8	0		
40	D	6	3 to 4	Yes	No	No	Yes	12	Yes	No	0	3	0		
41	J	15	Many	Yes	Yes	No	Yes	6	Yes	No	0	24	0		
42	D	10	3	Yes	No	Yes	No	12	Yes	No	3			Placed on daily injections after 1 year. Has had no recurrences since.	
43	D	8	3	Yes	No	No	No	18	Yes	No	2			Placed on daily injections after 18 months. No recurrences since then.	
44	D	12	2	Yes	Yes	No	No	17	Yes	No	2	9	0	2 hemorrhages while on treatment.	
45	D	6	2	Yes	No	No	No	12	Yes	No	0	10	0		
46	D	9	2	Yes	No	No	Yes	12	Yes	Yes	0	11	0		
47	D	8	3	Yes	No	No	No	16	Yes	No	1	(?)		Distress after 1 year from anxiety. Then placed on daily injections; no recurrences since.	
48	J	11	4	Yes	Yes	No	Yes	18	Yes	Yes	2			Hemorrhage after 14 months. Then placed on daily injections. Asymptomatic since.	
49	D	6	2	Yes	Yes	No	No	12	Yes	No	0	18	0		
50	D	10	2	Yes	No	No	No	12	Yes	No	0	16	0		
51	D	12	3	Yes	No	No	Yes	12	Yes	Yes	0	12	0	Hyperperistalsis Drafted after 11 months.	
52	D	6	2	Yes	No	No	Yes	11	Yes	Yes	0	22	0	No follow-up possible.	
53	D	6	3	Yes	No	No	Yes	10	No	No	2			Did not report for further treatment.	
54	D	5	1	Yes	No	No	Yes	7	Yes	Yes	0	24	0		
55	D & G	10	2	Yes	No	No	Yes	12	Yes	Yes	0	1	0	Drafted after 7 months. No follow-up possible.	
56	D	6	1	Yes	No	No	No	12	Yes	Yes	0	3	0	Gastric lesion healed at 3 months; duodenal at 1 year.	
57	D	5	3	Yes	Yes	No	No	4	No	No	1	6	1	Gastrorrhagia 1 month after discontinuing. Died 6 months later of cerebral vascular accident.	
58	D	12	2	Yes	No	No	No	12	Yes	Yes	0	1	0		

D = duodenal; G = gastric; J = jejunal.

difficulty traceable to colonic irritability, which has responded to management by dietary restriction and mineral oil.

Case 5. R. A., male, aged 38, an elevator mechanic, had established a diagnosis of peptic ulcer in 1939. At the time of starting injections on April 1, 1945, he was in acute distress, having experienced continuous attacks of varying severity during the preceding six years; X-ray examination revealed the presence of a crater on the lesser curvature of the stomach and a deformity of the duodenal bulb characteristic of ulcer. Relief from pain within a week was reported by the patient; in 5 months the gastric crater had disappeared. He has been symptom-free since the initial relief experienced; the X-ray examinations made after therapy reveal some residual duodenal deformity.

Case 6. F. H., male, aged 40, a sales executive, was first diagnosed as suffering from ulcer in 1935, and since that time experienced two acute exacerbations yearly, in the spring and autumn. Injections were begun on May 1, 1945, and continued for a year. At the outset of treatment the patient was in acute distress, for the relief of which he had voluntarily been hospitalized. Relief of pain within a week was reported, and the patient has been symptom-free throughout the course of injections and since their cessation on May 1, 1946. Initial X-ray studies revealed a duodenal deformity and crater, and hypertrophy of the rugal folds of the stomach; the roentgenological studies after treatment were interpreted as evidencing some residual duodenal deformity.

Case 7. R. N., female, aged 53, a housewife, was first established as suffering from duodenal ulcer in 1927, with continuous distress since. At the time treatment was begun on June 15, 1945, she was in acute pain and was hospitalized at her own request. On X-ray examination a large penetrating ulcer of the duodenum was evident; re-examination made one month after treatment was started revealed that the crater had filled. Her clinical course was complicated by frequent distressing accumulations of colonic gas, to which no definite pathological basis could be assigned, and which have been most resistant to any form of management. After three months of injections, during which X-ray rechecks had given no evidence of the original ulcer crater, she developed a lymphadenopathy in the inguinal glands, with pain down the right leg. It was considered possible that this was caused by the injections, and they were discontinued; in their place the patient was given medication in tablet form of a crude intestinal extract (which had been shown to protect the dog against the development of experimental ulcers (6)). An X-ray re-examination 4 months later revealed that the duodenal crater had returned, and the series of injections was resumed in February 1946 and is at this date continuing (Plate I).

Case 8. F. W., male, aged 49, a business executive, was first diagnosed as suffering from duodenal ulcer in 1927, and experienced continuous distress since that time, with a history of two major hemorrhages in 1934 and 1943 and a perforation in 1944, at which time a gastroenterostomy was done. This procedure failed to relieve his pain and discomfort. At the time injections were begun there was no evidence of a marginal ulcer, but a niche and deformity in the duodenal bulb indicated the

continued presence of activity there. Injections were made from July 2, 1945, until July 1, 1946; symptomatic relief was reported within a week and has continued without interruption. Post-treatment X-ray studies reveal the presence of some residual duodenal deformity; the gastroenterostomy has functioned well throughout.

Case 9. J. K., female, a housewife, aged 33, was diagnosed as having a duodenal ulcer in 1939, with a history of 5 or 6 acute exacerbations a year featured by epigastric pain, nausea, and vomiting. Duodenal irritability, with no particular deformity, was noted on X-ray examination at the beginning of treatment in March, 1945; a typical ulcer response to the Roth-Ivy caffeine test meal (7) was noted. Relief of symptoms has been manifest uninterruptedly since one week after the start of ther-

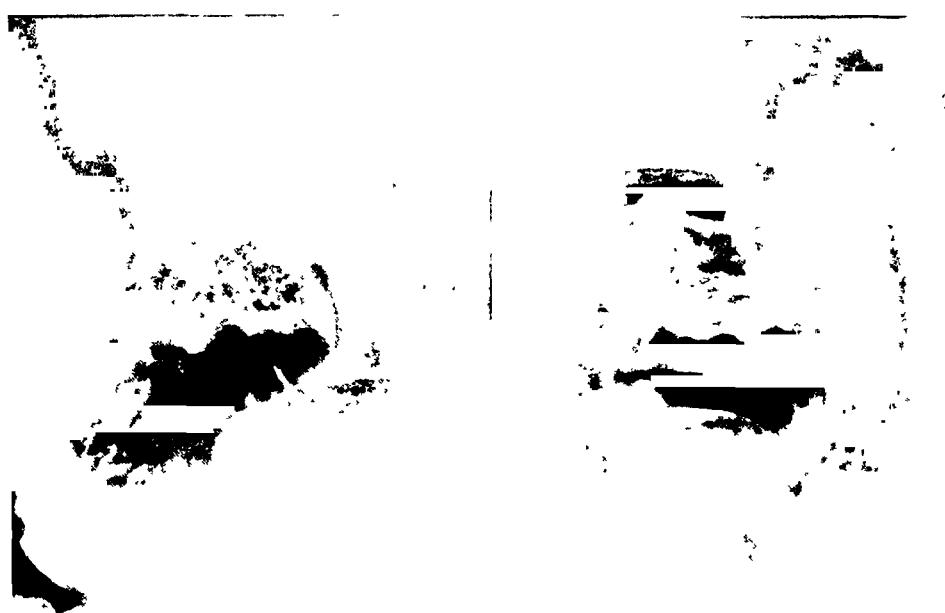


PLATE I

FIG. 1. Compression film of duodenal bulb (Case 7) at time of beginning treatment.

FIG. 2. Compression film of duodenal bulb after 7 months of treatment, indicating disappearance of crater and improvement in filling.

apy, and the upper gastrointestinal tract has remained radiologically normal. At the completion of the year's course of treatment, she underwent a hysterectomy for treatment of endometriosis, and has also been treated for infectious mononucleosis. Neither condition has affected the status of the ulcer, and a recheck on the caffeine test meal performed four months after completion of the course of treatment has given a response in the normal range.

Case 10. P. M., male, a radio station technician, aged 30, had assigned a diagnosis of peptic ulcer in 1936. He had since experienced two acute exacerbations of pain and distress in the spring and autumn of each year, with sour eructations throughout. Relief of distress was reported two weeks after injections were started on June 20, 1945, and no attacks have been experienced since, though the acid eructations have

persisted. X-ray evidence of improvement has been manifested; the films taken at the beginning of treatment showed a duodenal niche and deformity and those at completion some residual deformity.

Case 11. H. W., male, a janitor, aged 36, presented himself in severe pain with a duodenal ulcer first diagnosed in 1940. Injections were begun on May 10, 1945; five days thereafter his symptoms were relieved, and he has been uninterruptedly free of distress during the year's course of treatment and since its completion. His first X-ray examination revealed the presence of duodenal deformity and crater; his most recent, a filling of the crater with residual deformity.

Case 12. L. L., male, a business executive, aged 44, was diagnosed as suffering from peptic ulcer in 1939, with two seasonal exacerbations yearly. X-ray studies made shortly before the beginning of therapy on August 1, 1945, revealed the presence of a pyloric niche. He was free of distress one week after injections were started, and has remained so during and since the course of treatment, which was discontinued after six months on February 1, 1946. All radiological re-examinations made since the start of treatment have resulted in normal findings.

Case 13. T. W., female, a housewife, aged 44, had had a diagnosis made of duodenal ulcer in 1923, and experienced 3 to 4 acute exacerbations a year since that time. Injections were begun on August 20, 1945, and continued until February 20, 1946. Symptomatic relief was reported 10 days after the start of treatment, with no recurrences since. Radiological studies at the inception of treatment evidenced a typical clover-leaf deformity of the duodenal bulb, which was definitely improved on the post-injection films.

Case 14. J. T., male, a printer, aged 59, was first diagnosed as a case of duodenal ulcer in 1899, at the age of 12. During the intervening 47 years before he reported for treatment late in 1945, he suffered numerous acute exacerbations every year, worst in the spring and fall, with numerous episodes of bleeding. Examination of the upper gastrointestinal tract by X-ray revealed a pylorospasm and a marked duodenal deformity, and these findings have shown no appreciable change during the nine months that this patient has been on therapy. However, relief of pain and distress was reported within two weeks, and the patient has been symptom-free during the course of injections with the exception of two minor attacks, the first of a week's duration occurring a month after the start of injections, and the second of ten days' duration, six months later. Neither of the attacks was of severity comparable with those in the pretreatment period.

Case 15. R. C., male, a business executive, aged 47, was diagnosed as having a duodenal ulcer in 1939, and prior to reporting for injections on October 15, 1945, had suffered two to three acute exacerbations yearly; at this time X-ray examination revealed the presence of a duodenal deformity and niche. His previous attacks were featured by pain and distress and occasional bleeding; at the time injections were started he was asymptomatic, and has remained so during the ensuing 9 months of injections. A considerable improvement in the roentgenological appearance of the duodenum was manifest one month after treatment was begun, and the most recent rechecks have yielded essentially normal findings. In this interval the patient has gained about 30 pounds.

Case 16. R. M., male, an attorney, aged 33, was first diagnosed as a case of duodenal ulcer in 1935 and had suffered continuous discomfort since in the form of pain and frequent vomiting. At the inception of treatment on November 5, 1945, a duodenal niche and deformity were visualized by X-ray, together with a marked pyloric obstruction so that most of the opaque meal was retained in the stomach. The injections were supplemented with atropinization for three weeks; at the end of a month, the retention was definitely less and the patient's condition generally improved. At 5 months there was minimal retention and filling of the niche on X-ray examination, and apparently considerable ground had been won; however, a month later the retention returned in exaggerated form, possibly precipitated by a day and night of unwonted activity. The present status of the ulcer is not known, since on the most recent X-ray examination gastric retention of the barium meal was complete and the duodenal bulb not visualizable.

Case 17. H. G., female, a housewife, aged 33, first had a diagnosis of duodenal ulcer made in 1935. In the succeeding 10 years she was subject to 2 to 6 acute exacerbations per year, except during the course of three pregnancies, and during this time had several severe hemorrhages. At the beginning of injections in December 1945 she was receiving injections for undulant fever, as well as parenteral liver extract for her anemic state; the latter was discontinued; X-ray examination revealed the presence of a duodinal deformity and crater. Some relief from distress was reported 3 weeks after injections were started; during the ensuing seven months there has been no essential change in the roetgenological configuration of the duodenum and the patient has suffered one hemorrhage, occurring four months after treatment was begun, and of a severity measurably less than the preceding ones.

Case 18. M. C., male, a pharmacist, aged 44, reported for treatment late in December 1945, ten years after the presence of an ulcer had first been diagnosed. At the time injections were begun, a duodenal deformity was noted on X-ray examination, together with a penetrating ulcer, and a niche approximately 4 centimeters in diameter; there was continuous distress over a period of years, prior to treatment. Relief from distress took place gradually over a two-month period after parenteral enterogastrone therapy was started; and after six months the crater was noted to have filled.

Case 19. E. G., female, a secretary, aged 53, was first diagnosed as suffering from a duodenal ulcer in 1936, and prior to reporting for treatment she had experienced 3 to 5 exacerbations per year. When injections were begun on Feburary 1, 1946, pain and distress were present, which disappeared in 10 days. Radiological examination at the beginning of injections revealed the presence of a duodenal deformity and a fleck; the findings were essentially unaltered four months later. During this interval the patient has remained asymptomatic.

Case 20. C. C., male, a business executive, aged 46, experienced continuous distress since 1938, when the diagnosis of duodenal ulcer was first established, with occasional episodes of bleeding, and frequent vomiting. Late in 1944 a gastrojejunostomy was done, with relief of symptoms lasting for less than a year. In the summer of 1945 there was a return of distress and X-ray studies revealed the presence of a residual duodenal deformity and of a gastrojejunal ulcer. Injections were

begun on February 1, 1946, and relief from pain was reported in two weeks; there was a return of the distress three months after treatment was begun, for a period of 3 weeks. Radiologic examinations during the period of comfort revealed no evidence of a marginal ulcer; however, a recheck during the recrudescence of symptoms revealed its reappearance.

Case 21. F. A., male, aged 30, a salesman, suffered 2 to 4 acute exacerbations yearly, featured by pain and distress since 1938, when a diagnosis of duodenal ulcer had first been established. Radiologic examination at the start of treatment on February 15, 1946, revealed a constant deformity of the duodenal bulb compatible with a diagnosis of duodenal ulcer. Symptomatic relief was reported to obtain in 10 days; an X-ray re-check at 3 months revealed a duodenal bulb of essentially normal configuration.

Case 22. E. D., male, aged 50, a manufacturer, had suffered two to four acute attacks yearly since the initial diagnosis of duodenal ulcer, first established in 1930. At the time injections were begun on October 15, 1945, X-ray examination revealed a marked deformity of the duodenal bulb and a small crater. Relief from the acute symptoms was reported after one month, and X-ray rechecks since the treatment was established have shown a disappearance of the crater and amelioration of the deformity.

Case 23. F. C., male, aged 50, unemployed, had had a diagnosis of duodenal ulcer made in 1941, since which time he had suffered continuously from epigastric distress and frequent vomiting. At the inception of treatment on March 15, 1946, the retention of gastric contents was extreme, and the duodenal bulb not visualizable radiologically; a caffeine test meal administered at this time showed a very large residuum, and no evidence of excessive acid production. Three weeks later he reported considerable relief from the obstructive symptoms, and this has continued; and repetitions of the caffeine test meal have yielded findings compatible with the presence of a duodenal ulcer. The patient has gained considerable weight in this interval. However, on two repeat X-ray examinations, it has remained impossible to observe the progress of the opaque meal beyond the pylorus.

Case 24. G. J., male, aged 51, a stockbroker, had experienced two acute attacks per year since a diagnosis of duodenal ulcer first established in 1936. He was suffering from pain and distress at the time injections were begun on February 15, 1946, and X-ray evidence of a duodenal deformity and crater was noted. Symptomatic relief was reported within two weeks, and an X-ray recheck at the end of three months showed no evidence of the crater.

Case 25. E. S., female, aged 36, a saleslady, experienced one acute attack a year since the initial diagnosis made in 1937. Injections were begun on November 15, 1944, and continued for a year. She became asymptomatic one week after injections were begun and has remained so during the course of injections and for the ensuing eight months. Radiological studies at the beginning and end of treatment revealed a duodenal deformity, essentially unaltered through the period of observation.

Case 26. J. L., female, aged 35, a dental assistant, had suffered from three acute attacks per year since the initial diagnosis was established in 1939. Injections were

begun on September 10, 1945, and relief from distress was reported at three days. The patient has remained symptom-free since; the duodenal deformity noted at the outset of therapy has remained essentially unchanged.

Series 11—Three injections per week. This series includes 32 patients, all with histories dating back 5 to 15 years before therapy.

Case 27. M. J., female, aged 50, a housewife, manifested continuously moderate pain and distress since the time of an initial diagnosis of duodenal ulcer made in 1932. Relief of symptoms was reported three weeks after starting injections on April 1, 1943; and during the year of injections plus the ensuing 27 months the patient has remained asymptomatic. Roentgenographically there was a duodenal deformity and niche at the time treatment was begun, and no evidence of ulcer at its termination. A recheck in April 1946, two years after completion of the course of treatment, likewise evidenced a normal configuration of the duodenum on X-ray examination (Plate II).

Case 28. L. G., female, aged 48, a housewife, had experienced more or less continuous pain and distress since 1938, at which time the presence of a duodenal ulcer had been established. Injections were begun on April 15, 1943, and continued three times weekly for a year. Symptomatic relief developed gradually over a period of three months, the X-ray appearance of the duodenum at the beginning of treatment was that of a duodenal deformity and with a niche, and at its completion of some residual deformity with disappearance of the niche. The patient has been continuously under treatment in the clinic for a venereal infection; she has been free of ulcer symptoms since the initially experienced relief, including 27 months off treatment.

Case 29. A. O., female, aged 43, a housewife, had experienced a constant dull epigastric ache and dyspepsia since 1937, at which time the presence of a duodenal ulcer had been diagnosed. Her history was complicated by the existence of cholecystitis and cholelithiasis, and her gall-bladder had been removed in 1940. Injections were begun on April 5, 1943, and continued at thrice-weekly intervals for a year. A gradual abatement of distress occurred during the first three months following the inception of treatment, and the patient has had no recurrences of distress since that time, including 26 months off of treatment. This patient possesses a badly diseased heart.

Case 30. E. K., male, aged 61, unemployed, had suffered more or less continuously with epigastric pain and anorexia since 1938, at which time the presence of a duodenal ulcer had been diagnosed. Injections were made thrice weekly for a year, ending in July 1944; symptomatic relief was reported two weeks after the start of treatment, and the patient has had no recurrences since then, including a period of two years since the cessation of injections. X-ray evidence of improvement was noted on the basis of filling of the crater and attenuation of the deformity manifested on the examination made at the start of treatment. At the termination of the course of injections he was practically anacid; in order to elicit the secretion of



PLATE II

FIG. 1 Roentgenogram of duodenal bulb (Case 27) at time of beginning treatment.

FIG. 2 Appearance of duodenal bulb at completion of a year's course of injections.

FIG. 3 Appearance of duodenal bulb two years after completion of treatment, with no radiological abnormalities apparent.

free acid in the gastric juice, a combination of 1 mgm. of histamine and 500 mgms. of caffeine sodium benzoate was required.

Case 31. F. S., male, aged 68, a laborer, had experienced constant pain and distress since 1930, at which time the presence of a duodenal ulcer had been recognized. At the time injections were begun on October 1, 1943, X-ray examination revealed the presence of spasm and deformity of the duodenal bulb, with a crater present. Injections were given three times a week for a year; there was a gradual abatement of symptoms during the first two months of treatment, and he has since remained free of distress through an interval including 20 months after treatment was stopped, with evidence of improvement in the X-ray appearance of the duodenal bulb in the form of filling of the crater and diminution of the deformity. He presents complications of arteriosclerotic heart disease and inguinal hernia.

Case 32. F. B., male, aged 62, unemployed, had noted constant distress, and had had one severe hemorrhage, since 1938, at which time a duodenal ulcer had been diagnosed. At the time treatment was begun on November 1, 1943, there was X-ray evidence of spasm and deformity of the duodenum. Symptomatic relief was reported two weeks after injections were begun; they were administered three times weekly for a year and then discontinued, at which time an attenuation of the deformity was apparent radiographically. The patient has remained free of ulcer symptoms to date, including a period of 19 months off of treatment. His condition is complicated by the presence of colonic diverticula and prostatism.

Case 33. L. S., female, aged 50, an office worker, suffered continuous pain and distress since 1936, at which time the presence of a duodenal ulcer was recognized. At the time injections were begun on a thrice-weekly schedule in February 1944, radiographic studies revealed the presence of a deformity of the duodenum and a crater. Symptomatic relief was reported after a month of treatment and there have been no recurrences since. At 7 months after starting treatment the crater was shown to have filled and the deformity to be minimal.

Case 34. F. F., male, aged 46, an advertising executive, had experienced almost continuous pain and anorexia, with two acute flare-ups a year, since 1928, at which time the presence of a duodenal ulcer had been diagnosed. Radiographic studies, made at the time injections were begun on a thrice weekly schedule in February 1944, showed a marked deformity of the duodenal bulb. There was a gradual abatement of symptoms during the first two months of treatment, and he remained free of distress for the remainder of the course of injections. At that time he left the city, and his present status is unknown.

Case 35. G. G., female, aged 60, a housewife, manifested more or less continuous pain and distress since 1935, at which time the presence of a duodenal ulcer had been recognized. At the time injections were begun on a thrice-weekly schedule on June 24, 1943, X-ray examination revealed the presence of a duodenal deformity and crater, with definite retention. She became asymptomatic ten days after treatment was begun and continued so during the period of observation. In December 1943 there was no roentgenographic evidence of peptic ulcer other than some persistence of delayed gastric emptying; at that time she left the city and her subsequent course is unknown.

Case 36. J. M., female, aged 62, a housewife, experienced constant pain and distress since 1939, at which time a duodenal ulcer had been recognized. Injections were begun on a thrice-weekly schedule on March 29, 1944, and continued for a year. X-ray studies revealed the presence of a deformity in the duodenal bulb, which was measurably improved on completion of therapy. Relief of symptoms was reported two weeks after treatment was begun, and the patient has been free of distress since that time, including 15 months off of treatment.

Case 37. J. K., female, aged 62, a housewife, was found to have a duodenal ulcer in 1939, and experienced constant distress since that time. Injections were begun on a thrice-weekly schedule on July 15, 1944, and maintained for a year; she reported gradual relief of distress during the first three months of injections and since then has been free of attacks, at this writing a year has elapsed since injections were terminated. X-ray examination revealed a deformity of the duodenal bulb which improved under treatment. This patient is quite obese, and in the clinic has been assigned a diagnosis of asthmatic bronchitis and psychoneurosis which apparently coexist with the ulcer history.

Case 38. C. F., female, aged 55, a housewife, experienced a constant dull pain and anorexia since 1932, at which time a diagnosis of duodenal ulcer had been made. A gastrojejunostomy had been performed in 1938, without relief from distress. When injections were begun on a thrice-weekly basis on September 1, 1944, a deformity of the duodenal bulb was apparent on X-ray examination, and the gastroenterostomy was noted to be non-functioning. The patient reported relief of acute distress a week after injections were started, and she has continued symptom-free throughout their course and for the 10-month period since their termination. Rechecks of the X-ray appearance have revealed some improvement in the deformity, with the opaque meal leaving only by way of the pylorus at all times.

Case 39. E. S., male, a mechanic, aged 33, had experienced two attacks of pain and distress yearly since 1929, at which time the presence of a duodenal ulcer had been diagnosed. At the time injections were begun on a thrice-weekly basis on October 15, 1944, there was X-ray evidence of activity in the form of a typical duodenal deformity with a crater. Relief from acute distress was reported four days after starting treatment; there was a recurrence five months later, lasting for three weeks, and since that time the patient has been free of distress, including a period of eight months since injections were stopped. Throughout and since the course of injections the roentgenologic findings have been essentially the same.

Case 40. J. C., male, 33, a clerk, experienced three to four acute attacks yearly since the presence of a duodenal ulcer was first recognized in 1939. At the time he reported for treatment on March 10, 1945 acute symptoms were present, which were relieved two weeks after injections were started on a thrice-weekly schedule. He has been symptom-free since throughout a period including four months since completion of the year's course of injections. Radiographic examinations revealed a deformity of the duodenal bulb and a crater; periodic rechecks have given no evidence of any change.

Case 41. B. L., female, aged 48, a housewife, had experienced constant pain, distress, and anorexia since 1928, at which time a duodenal ulcer had been recognized.

She underwent a gastrojejunostomy in 1936 and developed a gastrojejunal ulcer after 15 months. In 1939 a gastric resection was performed; she had a return of distress after a year, and in 1942 a second resection was done. When she reported for treatment on January 20, 1944, she was in acute distress, and radiographic examination at this time revealed the presence of numerous flecks at the site of anastomosis. Injections were made three times weekly, and symptomatic relief was reported in three months. The patient has since remained asymptomatic; however, at the end of six months she refused to return for further injections or examinations. X-rays at the end of the six month injection period revealed no essential change.

Case 42. J. L., male, 50, an office worker, experienced three acute exacerbations a year since the presence of an ulcer was noted ten years prior to the outset of treatment. At the time this was begun he was suffering pain and had lost considerable weight. Relief from distress was reported after two weeks of thrice-weekly injections, but subsequently the attacks recurred after two, four, and eleven months of treatment. Since November 1945 he has been receiving daily injections and remained asymptomatic. Radiographic studies have revealed a persistent duodenal spasm and deformity.

Case 43. T. M., male, aged 54, a salesman, suffered three acute attacks a year for eight years prior to reporting for treatment late in 1943. Relief from pain was reported three weeks after injections were begun; two recurrences were experienced; eight and seventeen months in the course of continued therapy. At 18 months the injections were stepped up to a daily schedule, and he has since been asymptomatic, X-ray studies at intervals have revealed a persistent deformity of the duodenum.

Case 44. J. V., male, aged 45, an executive, suffered two acute exacerbations a year featured by pain and frequent bleeding for twelve years prior to the time injections were begun in April 1943. Relief of pain was reported a week after the thrice-weekly schedule had been established; subsequently the patient suffered two hemorrhages, occurring at 5 months and 17 months during the period of continuous therapy. After the latter episode injections were made daily for a year; and the patient has remained symptom-free for the ensuing 21 months, including nine months off of injections. Radiographic examinations have revealed a persistently deformed duodenum, unaltered in appearance since the date treatment was begun.

Case 45. J. R., male, aged 34, a designer, experienced two acute exacerbations a year for six years prior to the start of injections in September 1944. Disappearance of pain was reported a week after treatment was begun, and he has been asymptomatic since that time, including a period of 10 months since therapy was stopped. Radiographic examinations have revealed a persistent defect.

Case 46. P. H., male, aged 51, a teacher, experienced two acute attacks yearly of pain and distress for twelve years previous to the outset of injections in August 1944. Symptomatic relief was reported in 9 days, and has continued uninterruptedly since that time, including a period of 11 months since cessation of therapy. X-ray studies revealed the presence of a deformity and fleck at the beginning of treatment, and no defect at its completion.

Case 47. W. H., male, aged 49, a salesman, had experienced three acute attacks

yearly for eight years before injections were begun; on treatment there was disappearance of pain in three weeks. After a year there was a recurrence, apparently precipitated by worry over a member of the family. The injections were stepped up to a daily schedule, and the patient has since been asymptomatic for an 11-month period. Radiographically, he manifests a persistent deformity, essentially unchanged during the course of treatment.

Case 48. F. S., male, aged 46, a salesman, reported for treatment eleven years after the presence of a duodenal ulcer had first been diagnosed. He had had a gastroenterostomy 3 years before treatment was started, and at the time injections were begun on a thrice-weekly schedule in May 1944 a gastrojejunal ulcer was present, with pain, distress, and bleeding. Relief from acute symptoms was reported in three weeks; the patient remained asymptomatic for 14 months of continuous treatment, and then suffered a hemorrhage. At 18 months the injections were stepped up to a daily schedule, and he has remained asymptomatic for nearly a year except for one recurrence of pain six months after the daily injections had been started. X-ray examination at the time injections were first started revealed a crater which filled after 3 months.

Case 49. P. M., male, aged 32, a motorman, experienced two acute exacerbations yearly since the first diagnosis of ulcer in 1938, featured by pain and distress, and two hemorrhages. Relief from pain was reported one week after the start of thrice-weekly injections in February 1944, and he has been asymptomatic since that time, including an interval of 18 months since the cessation of treatment. Radiographic examination has revealed a deformity of the duodenal bulb, essentially unaltered through the period of observation.

Case 50. M. A., male, aged 52, a salesman, suffered two acute attacks a year for 10 years prior to April 1944, when injections were begun. Relief of distress was reported within a week, and the patient has been uninterruptedly asymptomatic since, including an interval of 16 months since injections were discontinued. X-ray studies have revealed a persistent deformity, unchanged through the period of observation.

Case 51. R. S., male, aged 48, a salesman, had suffered 3 attacks of pain and distress yearly, prior to reporting for injections in July 1944. Symptomatic relief was noted within two weeks after treatment was begun and there have been no recurrences since, during a period of time including a year since therapy was discontinued. At the start of treatment there was X-ray evidence of a deformity and niche in the duodenum, which disappeared at 7 months.

Case 52. E. A., male, aged 35, an office worker, had suffered twice-yearly exacerbations featured by epigastric pain for six years prior to reporting for injections. Relief from pain was noted two weeks thereafter, and he was asymptomatic for the eleven months during which treatment was continued. At this time he was drafted, and his subsequent course during the ensuing 26 months is unknown. A duodenal crater present at the time therapy was begun was found to have disappeared on re-examination, which revealed no defect at the time he was called to the service.

Case 53. A. K., female, aged 35, a secretary, had experienced three acute exacerbations a year prior to the start of injections, over a period of six years. Relief of

pain was reported a week after the injections were started; this was followed by recurrences at five and at seven months. X-ray examination revealed a niche and deformity, and these persisted throughout the course of injections. At 10 months the patient ceased to report for further therapy.

Case 54. A. S., male, aged 30, a salesman, suffered from one acute exacerbation a year for a period of 5 years since the presence of a duodenal ulcer had been established. At the time injections were begun there was X-ray evidence of a fleck typical of the ulcer. Relief of symptoms was noted within a week, and the patient remained asymptomatic during the seven months that treatment was continued. At this time no defect was radiographically visualizable, and he was drafted. His subsequent course during the ensuing two years is unknown.

Case 55. B. C., male, aged 50, an attorney, had experienced two acute exacerbations yearly since the presence of ulcer was first diagnosed in 1935. At the time injections were started a deformity of the duodenal bulb and a crater on the lesser curvature of the stomach were visualized. Relief of distress was reported in two weeks, and the patient has been asymptomatic since that time, including one month off of treatment. Re-examinations of the X-ray appearance revealed a filling of the gastric crater in 3 months, and healing of the duodenal lesion at a year.

Case 56. R. Q., male, aged 35, a reporter, had experienced two acute attacks a year since the time of the original diagnosis in 1933. Relief of pain was reported a week after injections were begun, and the patient has remained symptom-free for a year on treatment and 3 months after its cessation. Radiological examination revealed a deformity of the duodenal bulb at the outset of treatment, and no evidence of activity at its completion.

Case 57. C. G., male, aged 46, a business man, had suffered three exacerbations a year for a period of 5 years prior to reporting for treatment characterized by pain and bleeding. At the time injections were begun he manifested a definite deformity characteristic of duodenal ulcer. Symptomatic relief was experienced a week after injections were begun; four months later he suffered from nocturnal pain, and did not report for further injections. One month thereafter he suffered a severe hemorrhage; and six months later he died of a stroke.

Case 58. A. E., male, aged 37, a steel worker, had experienced two acute attacks a year during twelve years since the presence of an ulcer has been established. At the time injections were begun he was suffering from pain and distress and manifested a deformity typical of duodenal ulcer. Relief of symptoms was reported three weeks after treatment was started, and the patient has remained asymptomatic during the ensuing twelve months on and one month off injections. X-ray recheck at the end of the treatment period revealed no evidence of activity.

General survey of the 58 cases. In Table III a condensed summary of the clinical course of the patients during and after the period of injections of enterogastrone concentrate is provided. Most of the patients complained of localized pain and soreness at the site of injection after the first few administrations; however, almost invariably they were easily tolerable within a week, and essentially unnoticed thereafter, even when a new site of injection was

selected. The latter became necessary in many individuals who developed areas of painless induration after an interval ranging from weeks to months. These indurated areas were noted to come and go, and soon ceased to be the object of any regard save their avoidance in making injections. At no time has an infection been produced at the site of injection, in a number of individual administrations now totalling many thousands. Five of the patients have reported some swelling and tenderness in the inguinal lymph glands lasting for a few days, with one exception (Case No. 7) where it was persistent and was considered of sufficient moment to interrupt the injections.

TABLE III

Summary of the clinical course of 58 patients during and following the course of enterogastrone therapy

SCHEDULE OF INJECTIONS	TOTAL NO. OF PATIENTS	PATIENTS HAVING RECURRENTS		X.RAY FINDINGS		POST- TREAT- MENT COURSE UNKNOWN
		On treatment	Off treatment	Improved	Unim- proved	
6 a week for 6 months	3	0	0	3	0	0
6 a week for 12 months	8	0	0	7	1	0
6 a week in progress	15	4	—	10	5	0
3 a week for 6 months	4	1	1	2	2	2
3 a week for 12 months	28	8	0	18	10	4

DISCUSSION

Animal experiments. An examination of the representation (Chart I and II) of longevity of the Mann-Williamson dogs provides an extension of the previously reported findings that the protection afforded by enterogastrone is a lasting one but not uniformly indefinite. Of a total of 15 animals surviving over a year after operation, two died with ulcers, 30 and 32 months after cessation of therapy; and this is of significance in that it refutes any possible assumption that an anatomical or functional adaption to the altered condition of the intestinal tract had developed. That such a supposition is unwarrantable is likewise demonstrated by the fact that when other effective therapy is employed such as aluminum hydroxide or phosphate, the healthy state of the animal does not outlast the therapy, no matter how long it is continued, and an ulcer develops promptly after its cessation.

Peptic ulcer in the human. In view of the very high percentage of freedom from recurrences during and after therapy and of reported improvement in the radiographic appearance of the upper gastrointestinal tract, a statement to the effect that in the 58 cases described here the parenteral administration of enterogastrone was not without beneficial consequences might be considered admissible. The expectation of recurrences in reports of more extensive

series of ulcer patients ranges from 60 per cent to 87 per cent in two years (7, 8, 9); most of the individuals discussed in the present series have not been followed for a very long period of time after stopping treatment but the total absence of recurrences constitutes a most encouraging finding.

The mechanism of the apparently enduring protection remains obscure. We have previously reported (10) that after "enterogastrone" therapy the secretory pattern of a Mann-Williamson dog to an alcohol test meal reverts to that of a normal animal; but it is unknown whether this is a result or a cause of the protection. A similar protective action has been demonstrated to be producible by the parenteral injection of urine concentrates (11, 12, 13), and this has been attributed to the presence therein of a principle designated "antelone", the effect of which is to produce fibroblastic proliferation, vascularization, and epithelialization of the intestinal mucosa. Conceivably, a similar agent may be operative in the concentrate used in the present work; certainly there is often fibroblastic proliferation at the site of injection, which may be due to a direct action of the material used. It should be pointed out that in our experience "enterogastrone" has no advantage over strict conventional antacid therapy for the production of symptomatic relief in an acute exacerbation; on the contrary, the latter procedure is to be recommended because it can be applied more intensively over a relatively short period of time, especially in a bedridden patient. At the start of our management of the patients we have not infrequently found it advantageous to combine parenteral "enterogastrone" with Al(OH)_3 or AlPO_4 .

We have stated previously, and at this point should re-emphasize, that it is most unlikely that the anti-ulcer effectiveness of the material employed in these studies is attributable to the action of enterogastrone as such, in the sense that enterogastrone connotes the hormone which suppresses gastric acidity. In the dosage employed in these studies the concentrate could be expected to exert such an effect for only an hour or two; and to an extent far from complete, particularly in a hypersecreting patient or dog. Moreover, such an action completely fails to account for the findings that the duration of protection far outlasts the course of injections, and so the evidence strongly points to the existence of another agency, either in the form of another action of enterogastrone or of another substance present in the concentrate used, which has such an effect. Support to this view is lent by the apparent protective effect in the dog of a crude acid extract of intestinal mucosa when given by mouth in adequate doses; the secretory-inhibitory effect of enterogastrone is not elicitable by its oral administration, and it has been shown (14) that concentrates subjected to peptic digestion are deprived of their potency. In other words, the concentrate employed exhibits a dual nature, one phase of which manifests the protective effect described above and is resistant to the action of pro-

teolytic enzymes; it is at present unknown whether it is an entity in itself, or an activity of enterogastrone which survives proteolysis.

General reactions to our "enterogastrone" Concentrate. The concentrate used in this work is not free of vasodepressor substances, and produces in the dog a measurable fall in blood pressure when the dosage employed in the human is injected intravenously. We have carefully avoided introduction of the material into a vein in the patients; however, it has accidentally occurred on two occasions, with production of a flushed face and weakness of about a minute's duration. In three patients therapy was discontinued because of a marked generalized urticaria; all of these individuals had a proven allergy to pork. No other effects have ever been noted, other than the previously mentioned local action; and the non-antigenicity of the concentrate is further emphasized in Case 7, where injections were resumed uneventfully after a seven months' lapse. The fact that the great majority of patients faithfully reported for injections throughout the specified time bespeaks a symptomatic relief transcending any discomfort or expenditure of time involved on their part.

SUMMARY

A method is described for the preparation of an enterogastrone concentrate of uniform potency and suitable for parenteral injection in the human. Therapeutic trial on 43 Mann-Williamson dogs, and on 58 patients suffering from proven peptic ulcer over a period of years, has demonstrated the probability that the material is effective in preventing recurrences during the period of its administration, and for a length of time thereafter of a duration as yet undetermined. The protection afforded cannot be explained on the basis of the action of enterogastrone in inhibiting gastric secretion, and the true nature of the agent concerned cannot be at present defined.

REFERENCES

1. GRAY, J. S., BRADLEY, W. B., AND IVY, A. C.: Am. J. Physiol., 118: 463, 1937.
2. GREENGARD, H., HANDS, A. P. GROSSMAN, M. I., AND IVY, A. C.: Fed. Proc., 2: 17, 1943.
3. HANDS, A. P., GREENGARD, H., PRESTON, F. W., FAULEY, G. B., AND IVY, A. C.: Endocrinology, 30: 905, 1942.
4. HANDS, A. P., GREENGARD, H., FAULEY, G. B., AND IVY, A. C.: Fed. Proc., 2: 18, 1943.
5. IVY, A. C.: Gastroenterology, 3: 433, 1943.
6. IVY, A. C.: Fed. Proc., 4: 222, 1945.
7. EMERY, E. S., AND MONROE, R. T.: Arch. Int. Med., 55: 271, 1935.
8. ST. JOHN, F. B., AND FLOOD, C. A.: Ann. Surg., 10: 37, 1939.
9. HOLLAND, A. L., AND LOGAN, V. W.: Am. Therapeutic Soc., 41: 86, 1941.
10. GROSSMAN, M. I., GREENGARD, H., DUTTON, D. F., AND WOOLLEY, J.: Gastroenterology, 2: 16, 1944.
11. BEAVER, D. C., SANDWEISS, D. J., SALTZSTEIN, H. C., FARBMAN, A. A., AND SANDERS, A. W.: Am. J. Clin. Path., 12: 617, 1942.
12. SANDWEISS, D. J., AND FRIEDMAN, M. H. F.: Am. J. Digest. Dis., 7: 50, 1940.
13. SANDWEISS, D. J.: Gastroenterology, 1: 965, 1943.
14. HARRIS, S. C., GRAY, J. S., AND IVY, A. C.: Fed. Proc., 1: 37, 1942.

INTESTINAL PARASITES IN SERVICE PERSONNEL IN THE SOUTH PACIFIC: WITH SPECIAL REFERENCE TO THE INCIDENCE AND TREATMENT OF STRONGYLOIDIASIS¹

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INTRODUCTION

During the year 1943, at a Naval Hospital in New Zealand, 2388 fecal specimens from 1371 patients were examined for ova and parasites under the supervision of an experienced parasitologist.² Most of the patients in the hospital during that period were men who had seen active combat duty in the South Pacific Islands, although a small number were attached to ships or to units en route from the United States.

This study in no way represents a comprehensive survey of the incidence of intestinal parasitism in service personnel in the area since most of the fecal examinations were performed because of the presence of intestinal symptoms. However, several hundred routine studies on patients with recurrent malaria were included.

This type of sampling does not give a true picture of overall incidence and any error would be expected to be in the direction of an increase over the average. Table I indicates the incidence of parasitism in the entire group while tables II and III show the relative frequency of occurrence of the various parasites.

It will be noted that the incidence of the various intestinal parasites is not greatly different from published series in the United States. This is somewhat surprising since many of these men had been living under poor sanitary conditions on islands where the native populations are known commonly to be infected with hookworm (85 per cent, Mumford and Mohr) (1). Considering this fact and also that troops were comprised of men from all parts of the United States, our figure of 8.5 per cent incidence seems gratifyingly low. The Medical Corps of the Navy has reported hookworm in 16 per cent of recruits from Southern States (2).

Similarly, the figure for amebiasis, 6.9 per cent, is not as high as might be expected. Kofoid et al. (3) reported an incidence of amebiasis of 4.3 per cent in troops at home as compared with 12.8 per cent in troops on foreign duty. The Naval Medical Corps (4) reports an incidence of amebiasis of 7.14 per cent in recruits and 23 per cent in men returned from oriental duty. Craig and

¹ Presented at the meeting of the American Gastroenterological Association, May 24 and 25, 1946, Atlantic City, New Jersey..

² I am indebted to parasitologist E. K. Markell, Lt. (j.g.) H. C., USNR, for compilation of the results of examinations made under his supervision. (U. S. Naval Bulletin, 44: 65, 1945)

Faust (3) collected reported studies on 60,491 individuals in the United States which showed an average incidence of 9.8 per cent.

Of interest is the low figure of infestation with *Giardia lamblia*. Belding (5) collected studies indicating an incidence of this parasite of from 6.9 to 12 per

TABLE I
Fecal examinations—January 1, 1943 to December 31, 1943

Total number of examinations.....	2388
Total number of patients examined.....	1371
Number of patients with intestinal parasites.....	375
Incidence of parasitism.....	27%

TABLE II
Pathogens

SPECIES	NUMBER OF CASES	INCIDENCE
Hookworm.....	116	8.58
E. histolytica.....	97	6.96
Trichuris.....	28	2.07
Giardia.....	26	1.92
Strongyloides.....	17	1.26
Ascaris.....	5	0.37
Isospora hominis.....	5	0.37
Enterobius.....	1	0.07
Hymenolepis nana.....	1	0.07
Taenia saginata.....	1	0.07

TABLE III
Non pathogens

SPECIES	NUMBER OF CASES	INCIDENCE
Endolimax.....	268	19.83
E. coli.....	166	12.33
Iodamoeba.....	42	3.10
Dientamoeba.....	19	1.40
Trichomonas hominis.....	7	0.51
Chilomastix.....	4	0.30
Enteromonas.....	2	0.15

cent in the United States. Our figure, 1.9 per cent, is probably related to the fact that a large proportion of patients in our group had been in malarial areas and had taken atabrine, a drug which has been shown to be highly effective in eradicating Giardia (6).

It would appear from this brief review that the incidence of intestinal parasites in hospitalized patients in the South Pacific was gratifyingly low in spite of the location and nature of the military operations involved.

STRONGYLOIDIASIS

Although the number of cases of infestation with *Strongyloides stercoralis* was small, they presented some interesting problems. Our previous experience with 3 long standing cases at the Graduate Hospital, Philadelphia, had indicated the difficulties in eradicating the parasite.

Of 17 patients found to have Strongyloidiasis, 11 were kept long enough to be treated, the others being transferred elsewhere. Seven of the 11 were treated personally by the author during the winter of 1943-44.

TABLE IV
Associated parasites

Hookworm.....	5
End. histolytica.....	3
Trichuris trichiuria.....	2
End. coli.....	2
Endolimax nana.....	2

TABLE V

Reason for admission.....	11 cases
Malaria.....	7
Amebic dysentery.....	1
Malnutrition.....	1
Abdominal pain.....	1
Gunshot wound.....	1

Origin. Determination of the time and place of infestation was impossible. Certainly since most of the men had had repeated attacks of gastro-intestinal symptoms. However, it is of interest that 7 of the eleven were Marines evacuated from Munda, New Georgia; three more Marines had seen duty on Samoa and Guadalcanal; one sailor had been aboard ship in the Solomons and had been ashore frequently.

Conditions on Munda were particularly favorable for the spread of parasitic diseases since the men frequently were quartered in abandoned native or Japanese camps where no sanitary measures had been carried out.

Multiple infestations were common in this group as is shown in Table IV.

Reason for hospitalization. Most of these men were hospitalized because of recurrent malaria, the parasitism being discovered on stool examination performed because of persistent abdominal symptoms. As is shown in Table V

there was one case each admitted for amebic dysentery, malnutrition, abdominal pain.

Symptoms. The chief complaint at time of fecal study was abdominal pain in 7, diarrhea in 2, persistent nausea and vomiting in 1 and no complaint in 1 patient.

There is little proof that these complaints were due to strongyloidiasis since most of the patients had other possible causes of symptoms. However, the complaints had continued after eradication of the associated parasites in many

TABLE VI
Chief complaint at time of study

Abdominal discomfort or pain.....	7
Upper left quadrant.....	2
Lower left quadrant.....	2
Epigastrium.....	1
Lower abdomen.....	1
Generalized abdomen.....	1
Diarrhea.....	2
Nausea and vomiting.....	1
No complaint.....	1

TABLE VII
Eosinophilia

PATIENT'S INITIALS	PER CENT EOSINOPHILES	ASSOCIATED PARASITES
F. A.....	0	E. hist.; E. nana; hookworm
C. S.....	6	Trichuris
L. R.....	9	Hookworm
J. S.....	10	Hookworm
J. P.....	14	Hookworm
S. G.....	19	E. hist.; trichuris
E. C.....	22	E. coli
G. M.....	31	E. hist.
E. K.....	42	None found
S. P.....	48	E. nana; hookworm
E. B.....	53	E. coli

instances and were largely relieved after successful treatment of the strongyloidiasis. This was particularly noted in the patient with persistent nausea and vomiting who previously had been successfully treated for amebiasis. There were other instances where the symptoms were relieved by eradication of the associated parasites before the strongyloidiasis was treated. In fact one man was returned to duty in good health and without complaints in spite of several unsuccessful attempts to eradicate the Strongyloides.

Eosinophilia. As indicated in Table VII, eosinophilia showed wide variation in these patients.

It is of interest that the patient without eosinophilia had an associated infestation with *E. histolytica*, hookworm and *E. nana*. The patient with 53 per cent eosinophilia had only *E. coli* in addition to Strongyloides.

Treatment. All patients except one in this series received gentian violet therapy. The one exception was seen at a time when this medication was not available. He was given courses of Caprokol, thymol and four days of sulfaguanidine before being transferred. His diarrhea persisted and the feces remained positive for Strongyloides.

The remaining ten patients received gentian violet in 1 grain enteric coated tablets, orally, three times daily. In two, the drug was discontinued after 6 and 12 doses respectively because of nausea and vomiting. A full course consisted of 50 doses. There were 3 apparent cures on oral medication alone. Five patients received one or more duodenal instillations of from 3 to 25 cc. of 1 per cent gentian violet solution. Three of these patients showed persistently negative stools and duodenal aspirates after one treatment. In two instances

TABLE VIII

Total number of cases.....	17
Number treated.....	11
Apparent cures.....	7
Parasites persisted.....	3
Not re-checked.....	1

repeated small doses were required because of immediate nausea and vomiting with larger amounts. One patient's stools and bile became negative after two instillations of 3 cc. of 1 per cent gentian violet; the other continued to pass larvae after 4 treatments. The results of treatment are summarized in Table VIII.

CONCLUSIONS

1. The incidence of pathogenic intestinal parasites in Naval and Marine personnel in the South Pacific area was not unusually great. This is gratifying in view of the high incidence in native populations in this area and the nature of the campaign.
2. Strongyloidiasis responds satisfactorily, in most cases, to treatment with gentian violet. Intruduodenal instillation of a 1% solution may succeed when oral medication has failed. In this series there were 3 who responded to oral treatment; 4 responded to intruduodenal instillation.
3. Eosinophilia is not a reliable guide to the presence or absence of intestinal parasites and is not indicative of the type of parasite present.

REFERENCES

1. MUMFORD, E. P., AND MOHR, J. L.: Am. J. Tropical Med. 24: 1, 1944.
2. Notes on Tropical and Exotic Diseases of Naval Importance, National Naval Medical Center, Bethesda, Md., 1943, p. 52.
3. Quoted by CRAIG AND FAUST, Clinical Parasitology, 2nd Ed. Lea and Febiger, Philadelphia, 1940, p. 48.
4. Ref. 2—p. 24.
5. BELDING, D. L.: Clinical Parasitology, D. Appleton Century Co., New York, 1942, p. 132.
6. MORRISON, L. M., AND SWALM, W. A.: Am. J. Digest. Dis., 6: 325, 1939.

SURGERY IN ACUTE PANCREATITIS¹

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INTRODUCTION

In spite of the tremendous number of recorded observations on acute pancreatitis, there has been and still is considerable confusion in the minds of most clinicians as to whether this disease should be handled surgically or medically. In an attempt to throw some light on this problem, it seemed desirable to review the evidence which has accumulated, particularly in the past decade, including some of my own experiences. By the term acute pancreatitis is meant a primary inflammation of the pancreas sometimes associated with biliary disease, but not the type secondary to such systemic conditions as mumps, diabetes, arteriosclerosis, nephritis or alcoholism. In most cases the disease presents a dramatic clinical picture with an acute, stormy onset consisting of severe abdominal pain in an otherwise healthy individual.

HISTORICAL SURVEY

As one views the extensive literature on acute pancreatitis, it is possible to detect 3 distinct periods. In the early or pathological period before 1900, practically all of the cases were observed at autopsy. With a few exceptions, but one type of disease was recognized, which we now call pancreatitis necrosis, or hemorrhagic pancreatitis. The pathological changes were described and classified by Reginald Fitz in 1889, just a few years after his notable study on acute appendicitis, which also, at that time, was encountered largely at the autopsy table. Unlike his prophetic therapeutic recommendations for early appendectomy in acute appendicitis, Dr. Fitz could foresee no strikingly effective surgical procedure in pancreatitis. He did make two comments as follows: "With the establishment of an omental peritonitis comes the opportunity for the surgeon. The possibility of the successful removal of the gangrenous pancreas is suggested by the healthy condition of a patient 17 years after he had discharged this organ from his bowels." The second period included the early decades of the present century when the disease was encountered at operation, often performed without a definite diagnosis. The mortality was exceedingly high, usually around 50 per cent, and as time went on a trend toward more conservative treatment developed. The third, or medical phase, began about 10 or 15 years ago, and represented a reaction to the high mortality which com-

¹ Presented at the meeting of the American Gastroenterological Association, May 24 and 25, 1946, Atlantic City, New Jersey.

monly followed operation. The case for the non-operative therapy was well summarized by Pratt in 1939.

Much of the confusion in the literature on the therapy of acute pancreatitis is undoubtedly due to the existence of at least two types of the disease, each strikingly different. In 1922 the German surgeon Zoepfle described 4 patients upon whom he had operated, in whom the pancreas was the site of an acute, edematous inflammation without any evidence of necrosis or hemorrhage. This gross diagnosis was confirmed by microscopic study of pancreatic tissue removed as a biopsy during the course of the operation. All of these patients recovered uneventfully. Although there were other isolated instances of a similar nature reported before this time (3), Zoepfle must be credited with recording the first detailed description of a type of acute pancreatitis which was not necessarily fatal and which was not accompanied by necrosis or hemorrhage. This observer believed that the pancreatitis he described was merely an early stage in the development of true pancreatic necrosis which for some reason was aborted.

In the succeeding decades following 1922, an increasing number of observations were made by surgeons who, at operation, saw an acute inflammation of the pancreas not associated with necrosis or hemorrhage, and a mortality which was either nil or very low. It is obvious that mortality will vary greatly, dependent upon which lesion is present. In the accompanying Table I are listed a few observations made at operation by surgeons who recorded their findings in terms of the 2 types of pancreatitis mentioned, with a corresponding difference in the mortality.

Another source of difficulty in evaluating the results of therapy has been the uncertainty in making a bedside diagnosis of acute pancreatitis. Because acute pancreatitis simulates so many other acute diseases, it is apparent that, with no accurate diagnostic means, one cannot really know whether one is dealing with this disease unless it is possible to observe anatomical changes in the pancreas. As long as this is true, it is obvious that results of therapy could only be evaluated (a) in patients who were operated on, or (b) in patients who died and came to autopsy. In other words, it was impossible to be sure of the diagnosis when non-operative therapy was followed by recovery. On the other hand, it was quite apparent that both forms of therapy frequently failed because a great many cases of acute pancreatic necrosis were observed at autopsy, among those who had been operated upon as well as those who had been treated conservatively.

The development and general use of a bedside method for establishing the clinical diagnosis of pancreatitis had tended to clarify the confusion regarding the natural behavior of this disease treated without operation. Systematic

studies on the diagnostic use of the serum amylase test were begun by the author in 1929 and continued for a number of years thereafter. In the accompanying Table II is listed the incidence of acute pancreatitis before and after 1934, when the serum amylase test began to be used extensively on the wards of the Barnes and St. Louis City Hospitals. Based upon these observations it soon became apparent that many patients with acute abdominal symptoms which subsided rapidly and spontaneously were actually suffering from the type of pancreatitis described in 1922 by Zoepfle. Clearly this type of disease,

TABLE I
Acute pancreatitis
Mortality following operation (during which the pancreas was examined)

AUTHOR	EDEMA		NECROSIS		YEAR
	Cases	Died	Cases	Died	
Abell (1).....	9	0	21	9	1938
Dunlop & Hunt (2).....	2	0	12	2	1938
Griesmann (7).....	9	0	63	22	1939
Morton (9).....	22	9	13	8	1940
Lewison (8).....	20	1	13	4	1940

TABLE II
Incidence of acute pancreatitis
At Barnes and St. Louis City Hospitals

1931	6
1932	5
1933	4
1934*	10
1935	17
1936	18
1937	14
1938	17

* Blood amylase test available as routine during 1934.

while it did not require operation, was apt to be followed by recovery even if operation were carried out.

Although study of serum amylase was decisive in establishing a bedside diagnosis of pancreatic inflammation, it did not differentiate between the two types of acute pancreatitis mentioned above. It is clear, therefore, that more accurate data must be obtained as to the effectiveness of conservative as against operative therapy. In other words, if the patient recovers without operation it is still impossible to be sure which type of inflammation was present.

PRESENT OBSERVATIONS

In analyzing our cases of acute pancreatitis, attention was confined to 17 proved instances of pancreatic necrosis, as shown by operation or autopsy. While the number of cases is small, a few inferences may perhaps be drawn from these experiences. In presenting the data, the cases will be classified into the following groups:

Group I. In the following case, conservative therapy was carried out on the basis of an incorrect diagnosis because the serum amylase was not measured. Had the diagnosis been made, conservative therapy would perhaps have been more effective in that plasma or blood transfusions would have been employed; however, operation might also have been carried out.

Case 1, a 73 year old man, entered the hospital with a history that 3 days before he had been stricken with acute epigastric pain, nausea and vomiting. The clinical diagnosis was coronary thrombosis, and he was treated accordingly, but died two days later. At autopsy the heart was found to be normal, but the pancreas was the site of extensive necrosis, hemorrhage and beginning suppuration.

Group II. In the following group of 5 cases of pancreatic necrosis, operation was carried out at various periods after admission. The fatal outcome in each case was not necessarily an indictment against surgical therapy, but the experience suggested several ways in which operation might have been more effective.

Case 2, is that of a 42 year old man. He entered soon after the onset of epigastric pain and was operated upon one month later. A subhepatic abscess was drained, but this procedure was obviously inadequate because at autopsy several days later this cavity communicated directly through the foramen of Winslow with an abscess in the lesser omental sac in the midst of which was the necrotic pancreas. The serum amylase was not measured until the third day after admission, when it was found to be normal; it later dropped to one-third of the normal.

Case 3, a 57 year old man, was admitted a few hours after an acute attack of epigastric pain and was operated upon 24 hours later with a mistaken diagnosis of intestinal obstruction because serum amylase studies were not made. Acute pancreatic necrosis was found and the lesser peritoneal sac drained; although the patient did fairly well, his wound disrupted 3 weeks later and in suturing it a subphrenic abscess was discovered and drained. The second operation was followed by death, which was attributed to myocardial disease.

Case 4, a 39 year old woman, was admitted after an acute onset 4 hours before. The serum amylase was high and conservative therapy was started. Because of increasing distension the patient was operated upon 2 days later, but died following laparotomy. At operation tremendous acute dilatation of the stomach was found, which obviously indicated that the gastric suction part of the conservative regime was inadequate.

Case 5, a 39 year old man, was admitted after an onset 12 hours before, and was treated conservatively for 3 days without a diagnosis. Just before operation, however, a serum amylase was taken and found to be elevated. At operation bloody peritoneal fluid was found, but unfortunately the patient died before the lesser peritoneal sac could be drained.

Case 6, a 44 year old woman, was admitted after an onset of acute abdominal pain 3 days before, and was operated upon soon after admission with a diagnosis of acute intestinal obstruction. No serum amylase test was made. The patient died immediately after spinal anesthesia was induced and before the incision was made. At autopsy the pancreas was the site of an acute hemorrhagic necrosis.

Group III. In the next group of cases we decided to treat all patients conservatively. In the following 3 instances of acute pancreatic necrosis, the diagnosis was made soon after admission by finding a high serum amylase. In one of the cases (*Case 7*) and in another in the group above (*Case 2*) a subnormal amylase value was found after 3 days. The subnormal value was unusual, and may prove to be indicative of pancreatic necrosis, inasmuch as we have never observed it in acute interstitial pancreatitis. The fall in serum amylase was quite similar to the fall previously observed in many instances of interstitial pancreatitis. However, the clinical progress in each of the 3 cases was quite different. Instead of showing gradual improvement, these patients remained quite ill in spite of what we considered adequate conservative therapy, which included parenteral fluids, continuous gastric suction, and plasma transfusions. All 3 persons died and at autopsy necrosis of the pancreas with extensive suppuration of the lesser peritoneal sac was found. These cases may be summarized briefly as follows:

Case 7, a 54 year old woman, with an onset 4 days before admission, who died 7 days afterwards.

Case 8, a 55 year old man, with an onset 3 hours before admission, who died 8 days later.

Case 9, a 61 year old man, with an acute onset 5 hours before admission, who died 11 days afterwards.

Group IV. In the following case of acute pancreatic necrosis, recovery followed surgical therapy. The experience, moreover, illustrates many of the difficulties encountered in a really severe case.

Case 10, a 24 year old woman, was admitted 36 hours after the acute onset. Because the patient showed evidence of a spreading peritonitis, she was subjected to immediate operation, even though there was considerable circulatory impairment, and the risk was obviously great. Transfusions of whole blood and plasma were given during and after operation. On opening the upper abdomen, there was a gush of turbid, bile-stained fluid, and evidence of an intense, general peritonitis. Many

areas of fat necrosis were visible in the omentum. The lesser peritoneal sac was opened widely through the gastrocolic omentum, and this permitted the escape of much more fluid which looked almost like pure bile. Indeed, the intensity of the inflammatory signs suggested a bile peritonitis. The pancreas felt soft and necrotic. In addition to drainage of the lesser peritoneal cavity, the gallbladder was drained after removal of several stones. Chemotherapy was given.

Subsequent to operation, residual abscesses formed which required trans-abdominal incision and drainage on 3 occasions, twice anteriorly and once in the left flank. In one of the abscesses was found a mass of necrotic tissue recognizable as pancreas. Recovery was eventually complete at the time of discharge 2 months after admission. It seemed clear that in this particular case neither conservative therapy nor inadequate operation would have prevented a fatality.

Group V. In 7 cases of acute pancreatitis the patients entered the hospital in profound circulatory failure and died within a few hours thereafter. Such instances might be listed as hopeless from the start, and it is unlikely that any form of therapy would avail, particularly when the patient is of advanced age, which was true in 4 of the patients in this group.

DISCUSSION

One of the difficulties in discussing the results of treatment of acute pancreatitis is the need for a definite bedside diagnosis on admission to the hospital. If all the patients with acute abdominal disease were suspected of pancreatitis and serum amylase measurements carried out, a certain diagnosis could nearly always be established relatively soon after admission. It takes little more than a half hour to determine the level of amylase in the blood. Unless the patient has been sick for many days, a high value will be found in all patients with acute pancreatitis, barring rare instances in which the parotid gland is inflamed, which will also give a high value.

Once the diagnosis is made soon after the patient is admitted, a plan for therapy can be made without the confusion of considering other conditions. However, the problem of differentiating acute pancreatic edema from necrosis still remains. It is probable that about 80 per cent or more of the cases will prove to be of the interstitial or edematous type or occasionally of the subacute type and may be expected to subside spontaneously. There is little dispute about the therapy or outcome in this group. Occasionally, however, the patient will actually be suffering from acute pancreatic necrosis, which is known to end fatally without operation. What is known of the bedside manifestations of this type of pancreatitis?

Three features may be mentioned, any one or more of which may be present. One is the appearance of true circulatory impairment. Shock is seldom part of the picture in edematous pancreatitis even when the pain is severe. When it

is present on admission or develops during the course of observation, shock should be considered as an indication of necrosis of the pancreas. A second feature of pancreatic necrosis is the tendency for the manifestations to be those of a spreading perforative peritonitis. A third characteristic of necrosis as compared with edema of the pancreas is the failure of the former to subside. If the patient's manifestations persist in spite of conservative therapy, suppuration of the pancreas should be suspected.

In a suspected case of pancreatic necrosis the question of operation must be seriously considered, unless, of course, it can be proved that conservative therapy is less likely to be followed by a fatal outcome. In other words, is there any evidence that acute pancreatic necrosis can subside without operation? This is a fundamental difficulty in any evaluation of non-operative therapy of diseases requiring an anatomical diagnosis. For example, any analysis purporting to show the results in non-operative treatment of acute appendicitis suffers from the uncertainty that all or even a majority of the patients studied were actually suffering from acute appendicitis. In the case of pancreatic necrosis there have been rare instances in which a pancreatic abscess has broken through the abdominal wall and drained spontaneously or in which a pancreatic cyst has followed an episode characteristic of acute pancreatitis. There is even the case mentioned by Fitz in which a patient passed a mass recognizable as necrotic pancreas per rectum, indicating that pancreatic suppuration had drained into the bowel wall. It may be that slight hemorrhage or necrosis of the pancreas may subside without suppuration and its consequent complications. On the other hand, it would seem justifiable to assume that extensive necrosis of the pancreas should be looked upon as a perforative lesion leading to peritoneal infection and thus either to suppuration or spreading peritonitis. As such it inevitably would require surgical help even if operation were confined to drainage of the site of perforation, i.e., lesser peritoneal sac.

From our observations as well as those of others it seems clear that operation to be adequate must at least provide satisfactory drainage or exteriorization of the necrotic pancreas which, of course, forms the posterior wall of the lesser peritoneal sac. Inasmuch as the pancreas has no capsule, but is merely covered by a thin layer of peritoneum, it is doubtful whether any incision into the organ itself is justified. No one has attempted to remove the necrotic or gangrenous pancreas, as suggested 60 years ago by Fitz. There is, however, some evidence that a simple cholecystostomy may be a useful procedure in diverting bile from the common duct to the outside. On the other hand, there is considerable clinical evidence that more extensive procedures such as cholecystectomy or drainage of the common duct will prolong the operation and increase the mortality.

It would seem wise on the basis of the evidence herein discussed to abandon

the view that acute pancreatitis is a universally non-operative disease. While operation is certainly not indicated in the vast majority of instances, it would seem advisable to study each case very carefully after admission, once the diagnosis has been made with the aid of serum amylase measurements. Those that obviously are subsiding will present no problem. Should the acute manifestations not subside, even though the serum amylase falls, the possibility must be considered that the patient is suffering from pancreatic necrosis which may require drainage of the lesser peritoneal sac. Those who are in profound circulatory collapse on admission present a grave problem, but must also be considered as possible candidates for surgical therapy, inasmuch as true shock is practically never seen in acute pancreatitis unless necrosis is also present. When operation should be carried out in these cases cannot be categorically stated. It is obvious that any patient in shock will withstand operation poorly; on the other hand, shock associated with progression of perforative peritonitis can often only be halted by operation. If it is clear that the patient is suffering from pancreatic necrosis either because of the appearance of circulatory impairment or of persistence or spread of peritoneal infection in spite of adequate conservative therapy, operation must be considered so that a few patients may be saved who would otherwise die. The answer to the question then of whether acute pancreatitis is a surgical or medical disease must be based upon careful study of the patient soon after his admission, aided by the clinical progress based on the differentiation between acute edema and acute necrosis.

The term pancreatic necrosis is used as a term of differentiation from acute edematous pancreatitis, and indicates actual destruction, usually including hemorrhage into and gangrene of the pancreatic parenchyma. The term fat necrosis, on the other hand, has no such significance. Pin point white areas of fat necrosis have been observed by the author and by many others in patients with simple interstitial or edematous inflammation of the pancreas, usually, however, localized to the pancreas itself or to the tissues immediately surrounding it. Extensive fat necrosis involving the great omentum, however, is practically always associated with a true necrosis and hemorrhage of the pancreas.

CONCLUSIONS

1. An unequivocal non-operative policy in all cases of acute pancreatitis will be followed by a fairly low total mortality, but will probably lead to the death of a few patients who might otherwise recover following an appropriate operation.
2. Operation is not indicated in patients with acute pancreatitis of the edematous or interstitial, but may be indicated in the necrotic or hemorrhagic type.

3. Since an elevated serum amylase is found and falls similarly in both types of acute pancreatitis, differentiation must be based upon the clinical appearance and progress of the patient. However, a continued fall to a value below normal has been observed only in patients with a proved pancreatic necrosis.

4. Operation, when indicated, must be adequate but not extensive, should assure efficient drainage of the lesser peritoneal sac, and be associated with adequate non-operative procedures such as gastric suction, blood and plasma transfusions and chemotherapy.

BIBLIOGRAPHY

1. ABELL, I.: *Surg., Gynec. & Obst.*, **66**: 348, 1938.
2. DUNLOP, G. R., AND HUNT, E. L.: *New England J. Med.*, **218**: 376, 1938.
3. ELMAN, R.: *Surg., Gynec. & Obst.*, **57**: 291, 1933; also **61**: 670, 1935.
4. ELMAN, R.: *J. A. M. A.*, **118**: 1265, 1942.
5. ELMAN, R., ARNESON, N., AND GRAHAM, E. A.: *Arch. Surg.*, **19**: 943, 1929.
6. FITZ, R.: *Med. Rec.*, **35**: 197, 225, and 253, 1889.
7. GRIESSMANN, H. D.: *Zeit. f. Chir.*, **252**: 19, 1939.
8. LEWISON, E. F.: *Arch. Surg.*, **41**: 1008, 1940.
9. MORTON, J. J.: *New York State J. Med.*, **40**: 255, 1940.
10. PRATT, J. H.: *Diseases of the Pancreas*. Oxford Medicine, Vol. III, Part 1, p. 500.
11. ZOEPPFEL, H. D.: *Zeit. f. Chir.*, **175**: 301, 1922.

ETIOLOGY OF CHOLECYSTITIS¹

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The last few decades have shown marked advances in our appreciation of biliary tract problems. The testimony of the surgeon, contributions of the physiologist, merciless scrutiny of the pathologist, careful compilation of the reactions of affected individuals, and improved roentgen and intubation technics have revised completely our knowledge of biliary tract disease, now known to be the commonest cause of digestive disturbance affecting the upper abdomen in later life. Some investigators have maintained that as many as 50 per cent of the population over the age of 50 are so afflicted. Studies such as those of Lieber seem to demonstrate that cholelithiasis, one of the two most frequently encountered problems of the biliary tract, increases almost arithmetically with age (Table 1).

There is no unanimity of opinion regarding either the cardinal factors in the production of biliary tract disease or the mechanism by which they operate. Until such information is available we shall have no logical basis for a system of therapy aimed at the control of the underlying factors. We know from extensive physiological data that we can influence biliary tract function, but the recent studies of Thomas and Snape² throw serious doubt on the importance of the terminal sphincter in gallbladder evacuation. We are now able to diagnose disease of the biliary tract with a fair degree of accuracy, but there is little evidence in the literature to correlate diagnostic studies, as cholecystography and duodenal intubation, with the actual changes in the gallbladder wall as revealed at operation. The work in which we are engaged at present shows how difficult it is to predict the degree of damage. Only by correlating a large number of careful preoperative studies with anatomic and histologic examination of the organ can we hope to reach more exact conclusions.

It is generally recognized that gallbladder disease, unlike peptic ulcer and some of the other organic diseases of the digestive tract, is intimately linked with general body economy and would seem to be part of a systemic or constitutional condition. This is often further complicated by numerous psychosomatic manifestations. The evidence has crystallized along three avenues of approach; namely, infection, stasis, and metabolic or physiochemical disturbances. Whether the primary fault is to be found in psychosomatic and psychiatric causes, general body alterations, infections, inflammations, sensitization,

¹ Presented at the meeting of the American Gastroenterological Association, May 24 and 25, 1946, Atlantic City, New Jersey.

² Thomas, J. Earl, and Snape, W. J.: private communication to Author, February 1945.

or even local changes affecting the various portions of the upper digestive tract is not clear from clinical inquiry, surgical observation or experimental investigation. It is also plain that certain infections can attack the gallbladder. The evidence regarding metabolic changes which alter the chemistry of the bile has already reached imposing proportions, and the question of stasis enters the picture sooner or later in most cases. Just what is the initial factor and where one begins and the others follow has not been determined. For that reason we have seen too much casuistry in argument and throughout the literature a willingness to draw insufficiently substantiated conclusions from incomplete data.

TABLE 1

Incidence of gallstones in 23,675 postmortem examinations performed at the Philadelphia General Hospital from January 1, 1920 to December 31, 1937 (after Lieber)

WHITE—MALES				WHITE—FEMALE			
Age group	Total no.	No. with stones	Percentage of stones	Age group	Total No.	No. with stones	Percentage of stones
20-30	315	4	1.27	20-30	325	11	3.4
30-40	643	14	2.17	30-40	474	36	7.59
40-50	1208	41	3.39	40-50	886	82	9.25
50-60	1734	113	6.51	50-60	954	201	21.0
60-70	2016	210	10.4	60-70	1258	345	27.3
70-80	1419	236	16.6	70-80	1029	326	31.7
80-90	417	83	19.9	80-90	307	111	36.1
90-	25	5	20.0	90-	28	14	50.0
BLACK—MALES				BLACK—FEMALES			
20-30	615	1	0.16	20-30	799	16	2.0
30-40	785	7	0.89	30-40	748	38	5.1
40-50	889	17	1.9	40-50	740	66	8.84
50-60	784	25	3.2	50-60	669	71	10.6
60-70	499	31	6.2	60-70	378	62	16.6
70-80	233	13	5.6	70-80	185	35	19.0
80-90	49	3	6.12	80-90	35	8	22.8
90-	5	1	20.0	90-	8	0	

Because of the limited number of experiments performed or shortness of the test periods, conclusions not in keeping with the evolution of the disease in the human subject too often have been drawn. Too many workers in experimental cholecystitis have demonstrated acute damage to the animal gallbladder but have failed to permit the development of chronic lesions so typical in man.

Those who believe infection to be the leading factor base their contention on: 1) the demonstration of infection at operation and the isolation of certain bacterial strains from these cases; 2) the production of experimental cholecystitis by injection of certain of these strains; 3) the fulfillment of Koch's postulates

in at least a limited number of cases in which the same organism produced identical pathology and was recovered from several generations of laboratory animals; 4) the similarity of lesions produced in animals to those occurring in the human; 5) that such strains are frequently found in aberrant foci in individuals suffering from biliary tract disease.

It is recognized that bacteria are capable of attacking any or all layers of practically any part of the digestive tract, and that bacterial infection by damaging certain portions of the gallbladder wall can in turn bring about alteration of function. Branch (1) in 210 cases reported 25 per cent of positive cultures; Deaver (2), 52 per cent; Moynihan (3), 37 per cent; Judd, Nickel and Wellbrock (4), 47 per cent; Brown (5), 30 per cent in mild cases and 75 per cent in marked cases; Rosenow (6), 79 per cent; and Wilkie (7), 84 per cent. Branch, Brown, Illingsworth and Johnson report a much higher percentage in acute cases. Elsewhere (8) we have discussed these data in detail. On the other hand, the evidence is rather conclusive that in more than one-half the operations for chronic forms of cholecystitis the gallbladders removed are sterile. This is not proof that the lesions were not primarily infectious; even as the blood cholesterol is not an infallible criterion in calculous cholecystitis, inasmuch as in certain proved cases the findings may actually be low instead of high. In experimental cholecystitis considerable damage often results from administration of an agent capable of affecting the gallbladder, and yet months later, at necropsy, an extensive sterile lesion may be found. It is altogether probable, therefore, that infections as well as metabolic disturbances are transient rather than permanent, and it is our belief that cycles of infection may occur precisely as do recognized cycles of hypercholesterolemia, resulting in focal involvement and often focal destruction with more or less damage to the organ.

Elsewhere we have discussed the production of experimental cholecystitis with various bacterial antigens, our attention having been directed particularly to one strain of the nonhemolytic streptococcus isolated from a patient suffering from cholecystitis and colitis. Over a ten year period we have injected this strain into nearly 700 animals. The last series includes animals inoculated with the antigen and subsequently treated with vaccine and filtrate from the same source. The results are summarized in Table 2. In Table 3 the incidence of cultural recoveries of the original organism is reported, such cultures being taken several months and even a year or more after the last injection of the viable antigen. It will be noted that only 8.9 per cent gave a positive culture from the biliary tract, although there was evidence to show that 68.3 per cent showed some form of gross lesion of the gallbladder. These same findings were observed with the previous series of animals submitted to the action of this organism. Apart from serial injections we know of no method by which

we can approximate the presence of a continuous focus which might show an affinity for the gallbladder.

The proponents of the metabolic theory have a broad field for investigation embracing practically every factor which directly or indirectly affects the function of the hepatic and biliary organs. They base their arguments on 1) the known changes which occur in the composition of the bile, blood and body fluids; 2) the experimental effect of altering the bile in the gallbladder, either by direct injection or intraductal cannulization with various normal and abnormal

TABLE 2
Gross pathology associated with gallbladder disease
Series of 224 animals, antigen 7

	NUMBER OF LESIONS	PERCENTAGE OF LESIONS
Gallbladder lesions, gross total.....	153	68.3
Gallbladder diseased, bile normal.....	86	38.4
Gallbladder diseased, bile abnormal.....	67	29.9
Gallbladder diseased, no coexistent disease.....	18	8.0
Gallbladder diseased, with concurrent kidney lesions.....	21	9.4
Gallbladder diseased, with concurrent joint lesions.....	55	24.6
Gallbladder diseased, with coexistent organic and joint lesions.....	59	26.3

TABLE 3
Positive culture recovery
Series of 224 animals

	NO.	PERCENTAGE
Animals with 1 or more cultures.....	37	16.5
Total positive cultures.....	55	24.5
Bile, cultures from.....	20	8.9
Joints, cultures from.....	16	7.1
Kidney or urine, cultures from.....	10	4.5
Other sources, cultures from.....	9	4.0

constituents of bile. However, actual clinical demonstration of such changes in human gallbladder bile is lacking. That such changes occur is altogether likely but the mechanism is not clear. Furthermore, no very satisfactory method exists today for a precise and adequate evaluation of bile acid and salts either in the bile or the body fluids (Sabotka (9)) and practically all existing methods are open to criticism (Horall (10)). Table 4 summarizes the numerous factors other than bacterial which have been considered in the etiology of cholecystitis.

Clinicians and investigators have been particularly impressed with the role of

bile and its ingredients. Under certain conditions bile salts can be exceedingly toxic when introduced into the body. Subcutaneous injection nearly always leads to tissue destruction and necrosis, compelling investigators to use the intravenous method for the study of these related substances. In our studies on the toxic effect of certain bile constituents (11), we found it practically impossible to inject them subcutaneously or intramuscularly without extensive cell death. The work of Macht and our own observations (12) have demonstrated a similar effect on plant cytology. Just why they should prove so toxic when introduced beneath the skin and yet be tolerated with impunity by the digestive tract is not understood.

Alterations in the mucosa should be the logical result of changes in the bile salt content of the gallbladder. The work of Aronsohn and Andrews (13, 14, 15, 16, 17) illustrates the effect of this change in producing experimental cholecystitis. They altered the contents of the dog's gallbladder by direct puncture, or intraductal cannulization and injection of more concentrated bile. This form of cholecystitis was more pronounced the greater the concentration of bile injected. These authors reported a bile salt cholecystitis produced by their so-called non-traumatizing technic, *the maximum effects of which were noted on the muscularis and the serosa, while the mucosa was relatively intact.* The outstanding effect on the serosa and the fact that the concentration of bile salts was little in excess of the 6 to 10 per cent ordinarily encountered in gallbladder bile is significant. Using the same technic in 55 dogs they were able to demonstrate the relative toxicity of the different bile salts. Desoxycholic acid and its salts were most toxic. Decholin was found to be nontoxic. Even alterations in the pH of the bile were a subject of communication by these authors, who showed that slight variations beyond those normally known were sufficient to account for some of the changes. The nature of the lesions was more or less similar in all of their studies and there seems little doubt that certain constituents of the bile at certain concentrations were capable of altering portions of the gallbladder wall. Aronsohn and Andrews, in discussing the general question of experimental cholecystitis, point out that "a temporary increase in bile salt concentration in the gallbladder brings about human cholecystitis." Even bile salts by intravenous injection, although highly toxic, were capable of inducing this effect. All these observations are significant inasmuch as they suggest a facile method of inducing cholecystitis, but the same type of lesion has been produced by other means, notably by injection of bacterial antigens such as we used. We have described elsewhere, in a histologic study of experimental cholecystitis, similar changes often markedly altering the subserosa with little or no effect on the mucosa. Apparently this type of lesion is one form of reaction of the organ to an external injury which if sufficiently repeated is capable of extensive structural damage.

TABLE 4

AUTHOR	TOPIC	METHOD	ANIMALS	NO.	DURATION	FINDINGS	REMARKS
Aronsohn and Andrews	influence varying pH on toxic effect bile salts on normal gallbladder	acid sol. pH3 injected into gallbladder	dogs	70 exp.			Toxic action of bile salts on normal gallbladder not affected unless pH exceeds normal range
2. Aronsohn and Andrews	relative toxicity bile salts on normal gallbladder	cannulation of common duct; injection into gall bladder	dogs	55 exp.		sometimes gangrene; bile peritonitis; thick wall edema of serosa	Desoxycholic acid most toxic; decho-lin non-toxic
3. Aronsohn and Andrews	mechanism acidification bile in gallbladder	cannulation common duct; bile collected under oil	dogs	7 liver bile; 12 gallbladder bile			Low CO ₂ reflects decreased pH. Liver bile high in CO ₂ . Concentration total base unchanged. Considerable loss of chlorides
4. Aronsohn and Andrews	toxic effect various concen. bile on dog's gallbladder	catheter introduction various concen. in vitro	dogs	32 exp.	not stated	more concen. the bile, the more severe the cholecystitis	Concent. more than one half often caused death
5. Aronsohn and Andrews	bile salt cholecystitis	authors' nontraumatizing technic	dog	16-16 controls	not stated	like human cholecystitis	Markedly thickened serosa; mucosa scarcely affected. Considering slight excess over normal 6-10% results significant
6. Womack and Bricker	experimental cholecystitis	ligation cystic duct and injection bile and its compounds	dogs, rabbits	50, 14	24 hrs. to several months	depend on conc. bile and the ingredient	When gallbladder emplied and saline replaced no important change. When cystic duct occluded changes depend on conc. Sodium desoxycholate most destructive

7. Andrews, Goff, Hirdina	effect pancreatic juice on absorptive mech., gallbladder	needle puncture catheteriza-tion ducts	dogs	19	4 days	mild changes gallblad-der	Presence pan. Juice causes marked dif-ferential absorp-tion of fats at expense of cholesterol. Pre-cipitation later
8. Stutz and Bauer	exper. study role of pan-creatic juice in gallblad-der dis.	punctured gallbladder, withdrew bile through fine cannula, inject. pan-creatic juice	dogs	3			Unable to confirm work of Wolter and Westphal
9. DiStefano	experimental cholecystitis	transduodenal cannulation of pancreatic juice	dogs	11		all animals showed some evidence chole-cystitis	Considers stasis im-portant factor en-abling pancreatic juice to exert its digestive action
10. Wolter	role of pancreatic juice in producing gallbladder disease	Inj. into gallbladder by cholecystostomy tube, cystic duct and common duct inj.	dogs	41	a few up to 187 days variable		In all cases prompt destructive action, non inflammatory necrosis, edema; others infiltration mucosa, changes in muscularis and serosa
11. Wolter	pancreatic juice in etiology of gallbladder dis.						Offers suggestion that all cases of cholecystitis are due to reflux of pancreatic juice
12. Wolter	further evidence that pan-creatic juice may be etio-logical factor in gallblad-der disease						
13. Cop and Doubilet	pancreatic reflux in causing gallbladder disease	not experimental					9 cases in which authors believe cause to be pancreatic reflux
14. Cop, Gerber and Doubilet	ditto	not experimental					Reports 3 cases acute cholecystitis associated presence pancreatic ferments in gall-bladder bile. Refers to Westphal's studies.

TABLE 4—Continued

AUTHOR	TOPIC	METHOD	ANIMALS	NO.	DURATION	FINDINGS	REMARKS
15. Bisgard and Baker	pathogenesis gallbladder disease and pancreatitis	duct obstruction	goats	25			Neither stasis of bile nor reflux pancreatic j. single factor but combination produced acute aseptic cholecystitis with complete or partial necrosis of gallbladder wall
16. Mann, F. C.	cholecystitis produced by chemical means	5 to 12 cc. Dakins solution intravenously	dogs and cats (dogs most satisfactory)			Inflammation begins immediately	Solution containing less than 0.35% chlorine seldom causes reaction. Exact chemical effect not known. Occurred whether or not cystic duct ligated.
17. Aronsohn and Andrews	nitrogen content bile of normal and diseased gallbladders						No apparent difference between normal and cholecytic bile
18. Aronsohn and Andrews	protein inj. gallbladder and reaction of gallbladder in anaphylaxis	cannula technic; inj. egg albumin sol. into gallbladder	dogs	15	killed after 48 hrs.	Thirteen showed recent active inflammation. Mucosa normal. Serosa edema; round cell infiltration muscularis	Reaction obtained not anaphylactoid
19. Aronsohn and Andrews	ditto	4 inj. 5 cc 6% egg albumin within 3 days, 6 days larger injection	dogs	3, 3 controls	killed 1 hr. after last inj.	Marked edema of G.B. wall	Suggests anaphylactic response.
20. Allemand	allergic cholecystopathies	6% egg albumin sol. inj. via saphenous or jugular v. for large doses	dogs	8		Acute congestion edema	Appeared to have elective action on gallbladder

21. Alvarez pseudocholecystitis apparently caused by food sensitiveness		Describes 4 cases suggesting biliary colic			
22. Deissler and Higgins Important physiological study on sensitized male guinea pigs					
23. Andrews and Hrdina hepatogenous cholecystitis studied dogs with biliary stasis due to ligation	25	24 hrs. to 2 months	7 out of 12 cystic ducts ligated, infected; 5 common d. all infected; 5 out of 6 (both ducts ligated) infected	Maintain that stasis favors prompt infection of bile from liver, duet ligation marked evidence cholecystitis and bacteria. Anaerobic bacteria constantly formed in liver. G.b. normal and sterile	
24. Andrews and Hrdina ditto	dogs				
25. Thorntson bacteriology of cholecystitis	rabbits and guinea pigs intramuscularly			Short	This work in main supports work of Rosenow on elective localization, and demonstrates that <i>Clostridium welchii</i> as commonly isolated from human gallbladder at operation for cholecystitis, and from normal dogs, is of low virulence and nonspore forming. Lowered resistance of tissues appear prerequisite to maintenance of virulence and spore-forming ability in vivo. Virulent and spore-forming <i>Clostridium welchii</i> may be injected intramuscularly (leg) in rabbit, and though wound heals, organism may be recovered after about sixth day in low virulence, without spore-forming ability, while control cultures <i>in vitro</i> retain their high virulence and formation of spores. Seven strains streptococci isolated, chiefly from walls gallbladder; 1 strain passed through four successive animal passages.

TABLE 4—Continued

AUTHOR	TOPIC	METHOD	ANIMALS	NO.	DURATION	FINDINGS
26. Patey	experimental production cholesterolosis	blood cholesterol raised by feeding inflammatory reaction produced by trauma	rabbits	19		Confirms results of Illingsworth that rabbit cholesterosis gallbladder similar to that in man can be produced by raising blood cholesterol and inducing chronic inflammatory changes. Exptl. condition result of direct deposit of cholesterol from blood in phagocytic cells similar to that which occurs in other inflamed areas, rather than through interference with a mechanism of cholesterol absorption.
27. Williams and MacLachlan	bact. obstr. cholecystitis	intravenous inj. organisms recovered from cholecystitis	rabbits	31	Few days to several months	Too short an interval in our experience. Authors did not believe that this work substantiated belief that bacteria were primarily responsible. Unable to obtain cholecystitis with <i>Staphylococcus aureus</i> .
28. Aronsohn, H. G.	exptl. bacterial cholecystitis	Transduodenal injection	dogs	36	Electrocuted 24 hours after inj.	Believe cholecystitis difficult to produce unless additional factor of trauma or stasis. Nevertheless 1 strain <i>Streptococcus hemolyticus</i> produce severe cholecystitis. Unusual method of procedure
29. Reinblatt	primary infection of gallbladder					clinical study. Four hundred gallbladders removed at operation. Forty per cent infected, mostly with <i>B. coli</i> and <i>S. hemolyticus</i>
30. Denton						describes pathology of 403 gallbladders, of which 215 were noncalculous. Author believes other factors than infection necessary to explain commonly observed lesions of gallbladder.
31. Cole, Novak and Hughes	exptl. production chronic cholecystitis by obstr. lesions cystic duct	partial obstr. cystic duct by flap	dogs	32	2 years for maximum effect	Believe overconcentration of bile salts, etc., and damage mucosa by toxic chemical effect; infection appearing late is probably secondary.
32. Andrews	pathogenesis of gallbladder disease	ini. emulsified bacteria through catheter in common duct	dogs			Bile salts in excess 1 to 2% above 6 to 8% concentration in humans could produce gallbladder lesion

33. Graham and Peferman	Lymphatic origin of cholecystitis	expresses belief in lymphatic spread from liver, in other cases hepatogenous, and perhaps occurrence of some by bacterial contact
34. Wanamaker	General discussion of cholecystitis. No experiments.	Believes gallbladder disease closely correlated with dysfunction of other organs, and secondary to general systemic conditions.
35. Cassidy	Believes lymph-borne infection responsible for cholecystitis.	No experiments
36. Gundermann	total nitrogen studies on gallbladder	found total nitrogen content of human gallbladder higher in cholecystitis
37. Beckelman	nitrogen content of gallbladder	concurred in above opinion
38. Cole and Rositer		discusses from clinical standpoint relationship of lesions of the cystic duct to gallbladder disease
39. Scellis		describes one case of bile duct anomaly as a factor in the pathogenesis of cholecystitis
40. Womack		general discussion referring to previous article (6), holding some of the components of bile as responsible for cholecystitis.

In the studies of Aronsohn and Andrews a 20 per cent solution of bile salts produced a tremendous reaction on the part of the gallbladder wall while a concentration as low as 8.7 per cent produced a distinct effect. Cholic acid and apocholic acid gave slightly weaker reactions than desoxycholic acid, and glycocholic acid had much less effect. Definite proof that such concentrations occur in the human gallbladder would seem to be lacking. There seems to be no doubt that bile salts are toxic agents but the factor causing undue concentration to the point of inducing severe tissue reaction is still a mystery. Nor is it proved by any of these studies that an initial bacterial factor may or may not be the part of the mechanism bringing about such changes.

A second and perhaps equally interesting subject for investigation is the status of the pancreatic ferments, which by gaining ingress into the gallbladder are capable of producing cholecystitis. Andrews, Goff and Hrdina (18), Stutz and Bauer (19), Di Stefano (20), Wolfer (21, 22, 23), and Colp and Doubilet (24) have studied the influence of pancreatic reflux in producing biliary tract disease. Andrews and his co-workers used needle puncture and catheterization in 19 dogs, the duration of the experiment being only four days, but pathological changes of mild degree were produced. Stutz and Bauer used only 3 dogs and injected the pancreatic secretion into the gallbladder. The animals were killed after a short time and showed marked edema of the wall. DiStefano used transduodenal cannulation in 11 dogs, all of which showed some degree of cholecystitis. Wolfer is perhaps best known for this type of work. He used several methods on 4 dogs, as direct injection through a cholecystostomy tube and injections through the common duct. The pancreatic secretion was obtained by cannulating the major pancreatic duct. Non-inflammatory necrosis with edema resulted. Colp and Doubilet reported 9 cases of human cholecystitis which they believed due to pancreatic reflux, and pointed out that the common duct is resistant but the gallbladder vulnerable to this reflux. In a further communication Colp, Gerber and Doubilet (25) reported 3 acute cases in which pancreatic ferments were found in the gallbladder. Wolfer makes the statement that in a dog, after the introduction of pancreatic secretion into the common duct for a short period, a definite cholecystitis followed which in a few cases was present one hundred eighty-six days later. It is therefore reasoned that a variable percentage of cases may show evidence of cholecystitis from the entrance of the pancreatic juice into the organ. This is an attractive theory but one which leaves considerable doubt in the mind of the clinician, who may inclined to wonder why if there is a reflux into the gallbladder the same reflux should not do even more damage to the pancreas. An eminent surgical colleague tells us that conditions necessary for such a reflux rarely obtain in the average case of cholecystitis. We are prepared to admit that such a reflux

might occur and do serious damage to the biliary tract, but that it is the explanation for the average case of cholecystitis is far from proven.

Duct obstruction has received more than passing attention. Bisgard and Baker (26) used goats for their experiments on obstruction of the common duct, both distal and proximal to the junction of the pancreatic duct. From the data obtained these authors concluded that neither stasis of bile nor pancreatic reflux alone was essential, but that the combination of both factors was almost invariably followed by permanent pathologic changes in the gallbladder. Cole, Novak and Hughes (27) obstructed the cystic duct in dogs by means of a flap, claiming that a maximum effect was obtained in two years. They believe that over-concentration of bile salts and damage to the mucosa by toxicchemical effects were responsible and that infection appearing late in the condition was probably secondary. Here again it is difficult to understand just what underlies the duct obstruction unless a purely mechanical factor, such as a sterile stone, existed. Clinically we are not interested primarily in the effects of duct obstruction but in the cause. It is what precedes rather than what follows obstruction which must furnish the clue.

Cole and Rossiter (28), discussing from a clinical standpoint the relation of lesions of the cystic duct to gallbladder disease, point out that "it would appear that acute inflammation of the cystic duct would be a frequent lesion, particularly since the lymphatics from the various abdominal organs pass so near the duct and are contiguous with it. The frequent presence of dense adhesions about the cystic duct supports this contention. It cannot be determined how frequently inflammation of the cystic duct spreads to the body of the gallbladder and vice versa." Graham and Peterman (29) likewise discuss the lymphatic origin of cholecystitis and express the belief that a lymphatic spread from the liver, and in other cases hematogenous invasion, perhaps bacterial or toxic, occurs. The lymphatic distribution is undoubtedly an important factor *inasmuch as the pathways of the lymphatics through the gallbladder wall converge toward the serosa and apparently concentrate toward the cystic duct.* The literature on experimental cholecystitis contains numerous references to thickening and damage to this region; and recorded observations on human specimens and our own experimental studies suggest that it is a vulnerable spot in the gallbladder wall.

Another interesting approach to the problem of gallbladder disease is that of anaphylaxis and allergy. Alvarez (30) discusses the so-called "pseudocholecystitis" apparently caused by food sensitiveness, and describes four cases resembling biliary colic. He calls attention to the work of Deissler and Higgins (31) who, in a strikingly original approach, sensitized male guinea pigs and after previous injection studied (1) the reaction of the empty gallbladder

when the vesicle was suspended as a strip in physiological salt solution and (2) when exposed to the pressure induced within when antigens (horse serum and egg white) were added to the bath; and (3) the reaction of the sphincteric mechanism at the duodenal end of the common duct when the antigens were added to the bath. Their observations warrant the conclusion that the biliary tract, including the gallbladder, may be sensitized to foreign proteins as well as any other organ and that vigorous contraction in the presence of an antigen will occur. These findings may explain previous observations that the gallbladder does not contract during anaphylactic shock. The gallbladder does contract but the inhibitory influence of the sphincter mechanism prevents the flow of bile into the duodenum. Aronsohn and Andrews (32) in their work on the injection of egg white into the gallbladder to increase the nitrogen content, injected 3 dogs intravenously with crystallized egg white within three days, each injection being 5 cc. of a 6 per cent solution. After a six day interval much larger amounts of the 6 per cent solution were injected. *Marked edema of the gallbladder wall was found at autopsy, while similar examination of controls was negative.* The authors believed that this was in the nature of an anaphylactic response.

The total nitrogen studies are neither clear nor significant. The variations in the nitrogen content of the bile are considerable. Gundermann (33) found the nitrogen content of the human gallbladder higher in cholecystitis, and apparently Boekleman (34) concurred in the same opinion. Our own studies (11) on the nitrogen content of the third portion (liver fraction) from duodenal intubation revealed rather marked changes in the liver fraction.

Our own interest in this subject dates back more than fifteen years, when we were interested in the role of bacteria in the production of ulcer. In the first series of studies we obtained 41 strains from various sources—nose, throat, teeth, bile, bowel, urine, and from operative specimens, the details of which have been reported elsewhere. Since then we have used over 100 antigens in about 1500 animals, but in all these studies we were never able to produce peptic ulcer, even with strains obtained from ulcers excised on the operating table. On the other hand we encountered strains which consistently produced lesions of the gallbladder, (8, 35, 36, 37) and in our last series, comprising 224 animals, all were infected by inoculation with the antigen. One third then received injections of vaccine and another third a filtrate made from the same source. Elsewhere (38) we shall report the final results of these experiments, as well as a complete histologic study of the findings.

Briefly, in the original investigation we were able to demonstrate evidence of cholecystitis in 22 per cent. Since then, with more exact control and modification of technic, in which smaller doses were given in greater number over

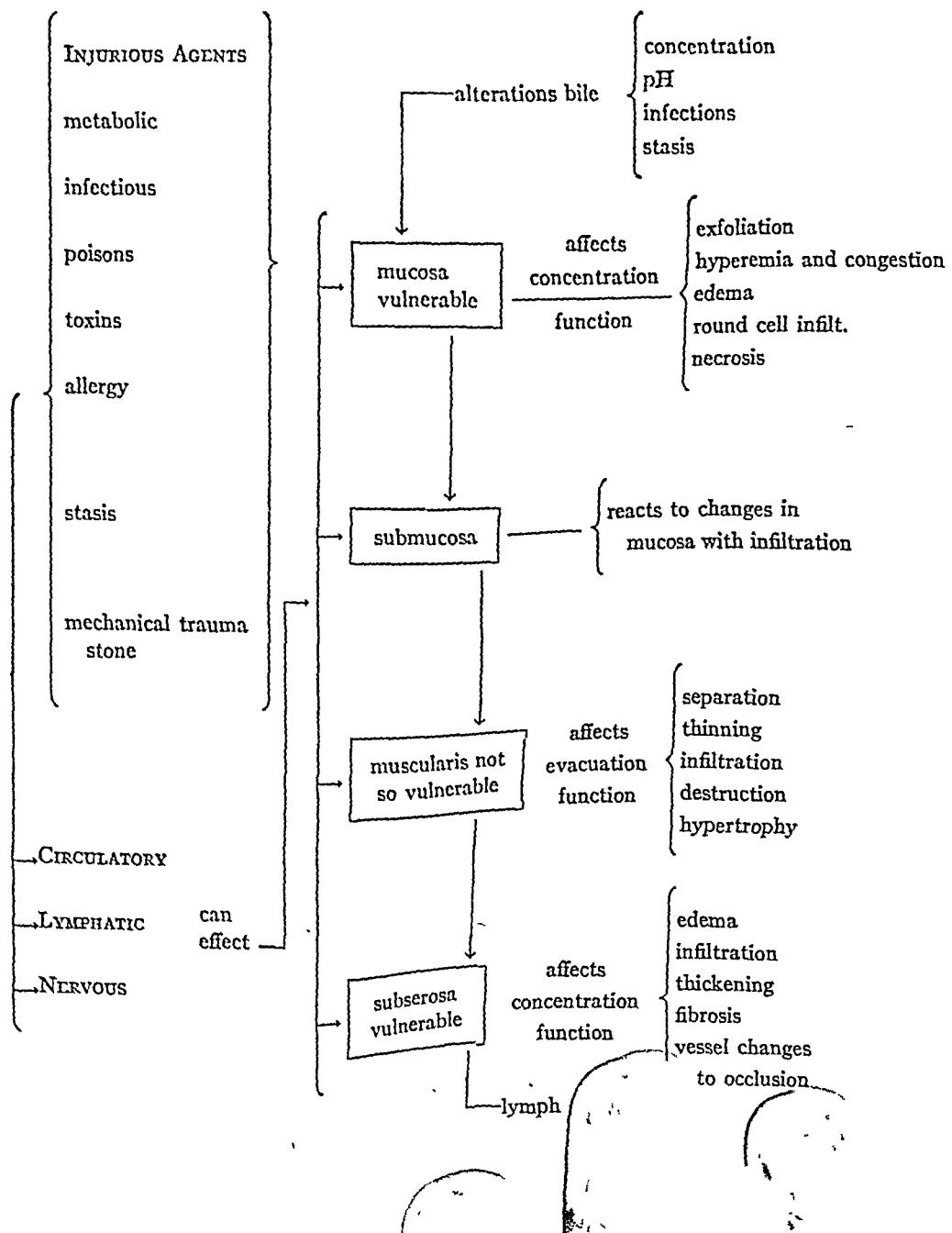
a longer period of time, we have been able to raise the incidence of cholecystitis produced to 68 per cent. Table 2 illustrates the incidence and other manifestations of infection. Inasmuch as these experiments often required several years, and the injection of the viable organism was usually completed after a three month period, it is not surprising that the number of positive culture recoveries was relatively small (Table 3). *It is obvious, therefore, that cholecystitis can follow a transient bacterial infection and that the subsequent changes emphasize the fact that structural damage of various grades may follow relatively few doses.*

The findings on bacteriologic study of the cultures made during the necropsy of this last series of 224 animals are of interest. Only 37, or 16.5 per cent, of the animals had an active infection in some part of the body, and only 20, or 8.9 per cent had a viable non-hemolytic streptococcus in the bile. Necropsy of large numbers of normal rabbits killed to obtain material for physiological and chemical studies had given us a clear picture of the healthy gallbladder; likewise our experience with experimental cholecystitis had taught us to recognize an unmistakably pathologic gallbladder. However, on some occasions during these studies necropsy revealed a gallbladder that was not definitely diseased yet on the basis of our previous experience could not be considered normal, and we therefore recorded them as "plus-minus". It is this questionable group which furnished the crucial data in the appraisal of bacterial therapy. For instance, 20 per cent of the vaccine-treated group exhibited a doubtful lesion, while only 4 per cent of the controls and 8 per cent of the filtrate group were so marked (38).

Briefly, the most important changes occurred in the mucosa and subserosa. Every form of gallbladder lesion seen in human pathology has been encountered—mucosal, muscular and serosal—varying all the way from mild catarrhal changes to gross involvement of the entire organ, with porcelain-like gross empyema and even calculous formation. Round cell infiltration, necrosis and even disappearance of the mucosa, diffuse edema, changes in the muscularis with diffuse interstitial involvement, separation of the muscular trabeculae, thinning out and in some cases hypertrophy were observed. *Perhaps one of the most significant changes was the marked thickening with edema, infiltration, fibrosis and thickening of the subserosa.* In both the experimental material examined in our studies and the human material to which I have had access the two most vulnerable parts of the gallbladder seem to have been the mucosa and the subserosa, and the least vulnerable the muscularis. I have just examined a series of 68 human gallbladders removed at operation, and almost without exception the commonest lesions are mucosal and subserosal. All those changes observed in human cholecystitis were seen in our experimental studies.

It is therefore apparent that lesions may originate not from a single source but as a result of multiple factors. Changes in the composition of the bile (in the pH and the concentration of bile acids), dissemination through the blood stream of bacteria and toxins, and finally the phenomenon of sensitization may cause damage to the gallbladder wall. We are convinced that under favorable conditions any or all of these mechanisms may play a role,

Mechanism of Gallbladder Disease



but there is little or no evidence to suggest that any one factor is universally responsible, nor is there any indication that a particular strain of bacteria is to be incriminated in the production of chronic cholecystitis. Bacterial infection would seem to be the most likely mechanism capable of inducing an acute change with tissue destruction in the absence of calculi. Gallbladder disease is nearly always secondary to disease elsewhere. Furthermore, the average individual is exposed repeatedly throughout his life span to infections, some of which may have an affinity for the gallbladder; but little is known of the influence of acute infections and infectious exanthemata in the production of disease of the biliary tract. Transient acute cholecystitis is by no means uncommon with many bacterial infections, and it is reasonable to suppose that certain organisms may exhibit a "tropism" for the biliary tract and that there are "cholecystotropic" strains.

It is obvious that therapy of any kind should be directed toward arrest of the acute lesion and control of the contributing factors by combating infection, regulating the metabolic mechanism, correcting biliary stasis, and preventing additional changes which might further damage the organ. Failing in these measures we then have recourse to surgery. Apart from elimination or control of the underlying conditions, we have in dietetic therapy our most effective means of influencing gallbladder function by reducing the demands on the organ, and in ordinary symptomatic care the handling of the various symptoms which constitute the gallbladder syndrome.

Regardless of the therapeutic method employed the dietary approach is of primary importance. Inasmuch as the function of the biliary tract is predominantly that of fat digestion, it is possible through alteration of this element of the diet to lessen functional demands on the organ during periods of inflammation or infection. Further, by judicious regulation of the intake of fat it is possible to favor restitution of function. The symptoms of the "biliary tract syndrome"—pain, indigestion, flatulence, gas—are all more or less amenable to symptomatic therapy.

If the acute lesion is due to some injurious agent, as infection, toxin or allergy, the detection and control of this factor must be an important one. I am convinced that many of the systemic infections, virus diseases, and local foci elsewhere, such as in the sinuses and tonsils, do play a part. These must be restrained and general systemic resistance fostered. Against infection we have all the bacterial therapy now available. The sulfonamides and penicillin are of value in acute biliary infections, the latter especially, as recent studies have shown that penicillin may reach a concentration in the bile exceeding that of the blood. Other foci in the head, urinary tract and elsewhere have their appropriate treatment. Carefully supervised vaccine, filtrate and other forms of bacterial therapy should be considered. The

metabolic aspect of the problem embraces the liver and the broad estuary dominated by the portal system, and the many available measures for modifying the bile entering the gallbladder may be employed. Not only is it possible to alter the bile but it is also probable that treatment of certain of the endocrine glands, notably the thyroid gland may be of importance in cholesterol metabolism. In the management of stasis we can fluidify the bile, check or lessen mucus production and insure restitution of normal function throughout the biliary tract, as by duodenal intubation and drainage.

Unless we control the underlying causes of biliary disease we can expect the gradual compromise of the gallbladder structure with eventual cessation of function. At present we have no precise method of predicting the extent of this damage. Many of the slower and more significant changes are not detected by duodenal drainage inasmuch as they occur below the level of the mucosa. Cholecystography, while a marked advance, probably reveals the gross changes only. It is to be hoped that in the future more rigorous control of technic and study of postoperative histologic findings may yield a formula for reaching more accurate conclusions.

CONCLUSIONS

1. There is no unanimity regarding the etiology of cholecystitis, either as to causation or mechanism of production.
2. The evidence available suggests the possibility of several active factors: infection, alteration of gallbladder contents (particularly the bile salts), reflux of pancreatic juice, lesions of the cystic duct (probably secondary), dissemination of bacteria or their toxins through lymphatic or arterial or venous channels, and sensitization. All these claims have received some support from experimental and clinical observation.
3. Practically every form of cholecystitis seen in the human subject has been observed in the experimental cholecystitis we have induced by injection of bacteria.
4. By alteration of technic and more frequent inoculations over longer periods we have been able to increase the incidence of experimental cholecystitis from 22 per cent in the initial series to 68 per cent during the past ten years of experimentation, and have observed the effect of a single antigen, the non-hemolytic streptococcus, in nearly 700 animals.
5. Any or all layers of the gallbladder wall can be affected in bacterial cholecystitis, the mucosa and subserosa being most vulnerable and the muscularis least so, as is true with human cholecystitis.
6. A chronic lesion may result from a single injection if the effect is sufficiently severe. In our experience, however, repeated injections over months has resulted in a marked increase in the chronic lesions.

7. Cessation of injections may result in arrest of the lesion.
8. The effect of this antigen is not specific for the gallbladder but produces lesions elsewhere, notably in the joints and some of the viscera.

9. There is evidence that bacteria or their toxins may focalize in any or all layers of the wall and may appear in the bile or in the rest of the biliary tract. Whether the action of such an antigen is that of a protoplasmic poison, a cell necrotic, a profound disturbance in cellular chemistry or enzymatic activity we are not prepared to state.

10. We are inclined to believe that cholecystitis may be an acute process but is more likely to be due to mild repeated infection acting slowly upon different parts of the gallbladder wall. That such changes may bring about or favor undue concentration of certain elements of bile, or produce a pancreatic reflux is not improbable. It is furthermore possible that bacterial sensitization may enact a role.

REFERENCES

1. BRANCH, C. F.: New England J. Med., 201: 308, 1929.
2. DEAVER, J. B.: Amer. J. Med. Sci., 135: 37, 1908; ibid, 136: 625, 1908; Penna. Med. J., 39: 13, 1929; J. A. M. A., 95: 1641, 1930.
3. MOYNIHAN, B. G. A.: The Practitioner, 81: 830, 1908; Brit. Med. J., 2: 1597, 1908; ibid, 1: 345, 1912; ibid, 1: 8, 1913; ibid, 1: 1, 1928.
4. JUDD, E. S., NICKEL, A. C., AND WELLBROCK, W. L. A.: Surg., Gynec. and Obst., 54: 13, 1932.
5. BROWN, R. O.: Arch. Int. Med., 23: 185, 1919.
6. ROSENOW, E. C.: J. Infect. Dis., 19: 527, 1916; Coll. Pap. Mayo Clinic 1916, 8: 222, 1917; Surg. Gynec. and Obst., 33: 19, 1921; Ann. Clin. Med., 1: 211, 1923; International Clinics S.40, 2: 29, 1930.
7. WILKIE, D. P. D.: Brit. Med. J., 1: 481, 1928; ibid, 2: 37, 1929.
8. REHFUSS, M. E., AND NELSON, G. M.: Medical Treatment of Gallbladder Disease, Phila., W. B. Saunders & Co., 1935.
9. SABOTKA: Quoted by Horrall, O. H.
10. HORRALL, O. H.: Bile, Its toxicity and Relation to Disease, Chicago, 1938.
11. REHFUSS, M. E., AND WILLIAMS, T.: Am. J. Dig. Dis., 8: 407, 1941.
12. REHFUSS, M. E., AND WILLIAMS, T.: Am. J. Dig. Dis., 10: 435, 1943.
13. ARONSOHN, H. G., AND ANDREWS, E.: Proc. Soc. Exp. Biol. and Med., 34: 763, 1936.
14. ARONSOHN, H. G., AND ANDREWS, E.: Proc. Soc. Exp. Biol. and Med., 34: 765, 1936.
15. ARONSOHN, H. G., AND ANDREWS, E.: Proc. Soc. Exp. Biol. and Med., 33: 89, 1935-1936.
16. ARONSOHN, H. G., AND ANDREWS, E.: Proc. Soc. Exp. Biol. and Med., 34: 736, 1936.
17. ARONSOHN, H. G., AND ANDREWS, E.: Proc. Soc. Exp. Biol. and Med., 33: 87, 1935-1936.
18. ANDREWS, E., GOFF, M., AND HRDINA, L.: Proc. Soc. Exp. Biol. and Med., 29: 1091, 1931-1932.
19. STULTZ, E. AND BAUER, R., Presse med., 41: 1928-29, 1933.
20. DI STEFANO: Riv. de Pat. Sper. 24: 33, 1940.
21. WOLFER, J. A.: Surg., Gynec. and Obst., 53: 433, 1931.
22. WOLFER, J. A.: Surgery, 1: 928, 1937.
23. WOLFER, J. A.: Ann. Surg., 109: 187, 1939.
24. COLP, R., AND DOUBILET, H. D.: Ann. Surg., 108: 242, 1938.
25. COLP, R., AND DOUBILET, H. D.: Ann. Surg., 103: 67, 1936.
26. BISGARD, J. D., AND BAKER, C. P.: Ann. Surg., 112: 1006, 1940.
27. COLE, W. H., NOVAK, M. V., AND HUGHES, E. O.: Ann. Surg., 114: 682, 1941.

28. COLE, W. H., AND ROSSITER, P. S.: Am. J. Dig. Dis., 5: 576, 1938.
29. GRAHAM, E. A., AND PETERMAN, M. G.: Arch. Surg., 4: 23, 1922.
30. ALVAREZ, W. C.: Proc. Staff Meet. Mayo Clin., 9: 680, 1934.
31. DEISSLER, K., AND HIGGINS, G. M.: Am. J. Physiol., 112: 430, 1935.
32. ARONSOHN, H. G., AND ANDREWS, E.: Proc. Soc. Exper. Biol. and Med., 33: 85, 1935-1936; ibid, 32: 1631, 1934-1935.
33. GUNDERMANN: Mitt. a. d. Greuzzel. d. Chir., 39, 1936.
34. BOEKELMAN, A. J.: Klin. Woch., 25: 147, 1928.
35. REHFUSS, M. E., AND NELSON, G. M.: Am. J. Dig. Dis. and Nutr., 2: 593, 1935; ibid, 1: 759, 1935.
36. REHFUSS, M. E., AND NELSON, G. M.: Am. J. of Dig. Dis., 5: 571, 1938.
37. NELSON, G. M., AND REHFUSS, M. E.: Surg. Gynec. and Obst., 69: 129, 1939.
38. REHFUSS, M. E., AND NELSON, G. M.: Surg. Gynec. and Obst., (to be published).

Section on
**CLINICAL PATHOLOGICAL
CONFERENCES**
and
INSTRUCTIVE CASES

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CHOLECYSTITIS AND CHOLELITHIASIS IN IDENTICAL TWINS

JAMES TESLER, M.D.
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I was unable to find any reference to cholelithiasis in identical twins in the literature (1-5). I therefore wish to report the occurrence of this pathological process in identical twins as further evidence in support of a constitutional factor in the causation of gallstones.

CASE REPORTS

E. A., age 19, female, white, an identical twin, began to suffer from attacks of abdominal pains and vomiting in 1939, at the age of 14. At times, the attacks were accompanied by fever and on two occasions morphine was necessary to alleviate the pains. Between attacks she felt fine except for excessive belching and constipation.

In February 1944, the patient reported to my office. She then stated that for the past week she had been getting frequent attacks of pains in the right infra-scapular region radiating to the right upper quadrant. The pains were accompanied by vomiting and on one occasion morphine was necessary.

Physical examination. The patient did not appear acutely ill although she complained of abdominal pains and vomited while in the office. Abdominal examination revealed marked tenderness in the right upper quadrant. The temperature was 100.4 by rectum.

Past and family histories were non-contributory.

The clinical impression was cholecystitis and probably cholelithiasis.

A radiographic study of the gall-bladder in April 1944, using the double dye method, revealed a poorly functioning viscus with radiolucent shadows suggestive of calculi. A diagnosis of cholecystitis and cholelithiasis was made and surgery advised.

margin. No abdominal tenderness could be elicited. He had a right inguinal hernia. He was not jaundiced. Rectal examination was negative.

LABORATORY FINDINGS

Urine analysis: negative. Sedimentation rate: 56 mm. at the end of an hour. Blood count: RBC: 3,900,000, WBC: 13,150, Hb.: 12 grams. Poly. Neutro.: 67%, Eos.: 1%, Lymphs.: 32%. Kahn: negative.

CLINICAL COURSE

The patient was admitted to the Presbyterian Hospital on the twentieth of January, 1946. The esophagus was intubated and 225 c.c. of thick foul smelling partially liquid food and mucus were removed. No free acid was present in this fluid. A tentative diagnosis of achalasia of the cardia with associated upper abdominal disease was made. Duodenal ulcer, cholecystitis, hepatic cirrhosis, pancreatitis and gastric carcinoma were considered in the differential diagnosis. The esophagus was lavaged six times in the course of three days, but even after lavage no liquids would pass through. An attempt to pass a silk thread failed even though tried over a period of seventy-two hours, both with and without a leader of lead shot. His nutrition was kept up fairly well over a period of seven days by intravenous fluids which were given almost continually. The patient was constantly in pain severe enough to require morphine for relief. The pain was present both at the xiphoid and in the right upper quadrant but the patient was not tender in these areas. In view of our inability to get water to pass into the stomach it was deemed inadvisable and impossible to introduce sufficient barium into the stomach to obtain diagnostic X-ray films.

OPERATION

Pre-operative diagnoses. 1. Peptic Ulcer of esophagus with stricture. 2. Carcinoma of stomach. 3. Peptic ulcer. 4. Pancreatitis. 5. Cholecystitis. 6. Hepatic cirrhosis.

Exploratory laparotomy by Dr. Edward Sprague on the twenty-sixth of January 1946, revealed a golf ball sized mass in the head of the pancreas and a distended gall bladder with fresh adhesions surrounding the gall bladder and head of the pancreas. The duodenum appeared normal and no ulcer could be palpated. The stomach was very small in size. Dr. Sprague considered the mass in the head of the pancreas inflammatory in nature because it was soft to touch and because of numerous surrounding adhesions. The intra-abdominal esophagus appeared normal except that at the diaphragm the wall appeared edematous. No liver disease was evident. A gastrostomy was performed and feeding tube inserted.

Post-operative diagnosis. 1. Stricture of esophagus, probably due to peptic ulceration. 2. Sub-acute cholecystitis and pancreatitis.

The patient had a fairly normal immediate post-operative course. He was fed about three thousand calories daily through the gastrostomy tube. After



FIG. 1. LARGE ULCER OF DUODENUM

the fourth post-operative day the esophagus was lavaged twice daily. On the sixth post-operative day a small amount of water began to pass through the esophagus. On the same day the patient again began to complain of epigastric and right upper quadrant abdominal pain which required morphine for relief. Fats were eliminated from the diet without benefit. On the twelfth post-operative day, the seventh of February 1946, while awaiting an esophageal

lavage, the patient had a desire to move his bowels. As he rose from the toilet he collapsed in shock on the floor, fracturing his nasal bones. He was unconscious for fifteen minutes. On opening the gastrostomy tube fresh blood flowed from the stomach. Despite repeated transfusions of whole blood the patient



FIG. 2. DILATED ESOPHAGUS SHOWING MARKED HYPERTROPHY OF MUCOSA

could not be gotten in condition for further surgery and he died after fifteen hours.

AUTOPSY

Pre-autopsy diagnosis. 1. Peptic ulcer of esophagus; erosion of esophageal artery.

Autopsy was performed by Dr. S. A. Goldberg, pathologist of the Presbyterian Hospital.

Diagnoses. 1. Ulcer of the Duodenum, 5 c.m. in diameter, at the Ampulla of Vater with erosion of the pancreatico-duodenal artery which was calcified. (See Fig. 1.) The head of the pancreas was enlarged and this enlargement corresponded to the area of the duodenal ulcer. There was a mass of fresh adhesions about the gall bladder and head of the pancreas. Microscopic: A. Chronic Ulcerative Duodenitis. B. Chronic Pancreatitis. 2. The esophagus was markedly dilated and formed a fusiform sack beginning at the upper end of the sternum extending to the diaphragm. The entire mucosa of the esophagus was eroded. Microscopic: Chronic erosive esophagitis. (See Fig. 2.)

Immediate cause of death. Hemorrhage from eroded pancreatico-duodenal artery.

had always been nervous and was overprotective of the girl, who had always been quiet. She had never wanted to go out with boys. Under psychotherapy she improved.

Case 4 was that of a married woman forty-two years of age, who was usually tense. Her troubles started with the beginning of menstruation. The father was an unstable ne'er-do-well. As a child, the patient had two attacks of somnabulism, during which she tried to murder her mother. As she grew older, she resented the mother's interference in her affairs. She was frigid and refused to have intercourse with her husband. Psychotherapy was tried without results, because she had so little insight, and remained refractory and obstinate.

Case 5 was that of a married woman. Her mother was a demanding person and had never gotten along with her. The patient had to run the home and take care of her mother. She had slept in the room with her parents until she was fourteen because of her nervousness and fear of the dark. Her marital experiences were "horrible, disgusting and painful." The patient later developed a number of hypochondrial complaints.

Case 6 was that of a girl of twenty years. Her trouble started when she became engaged to a boy. The mother was domineering and ran the patient's life. The girl was dependent, shy, spoiled, socially retiring, colorless, tearful and submissive. She was afraid to get married for fear of sex.

Case 7 was that of an unmarried woman who had been sick for fifteen years. Her mother was domineering and the patient was "mother's baby." The mother objected when the girl had her first love affair, so it was given up. All social life was also given up so that she could serve the mother. She contemplated suicide. She had little sexual reaction to men, being always frigid. She underwent psychoanalysis and eight electric shock treatments, but soon returned to her former mental pattern of life. She had very little insight into her trouble.

Case 8 was that of a married women of thirty. Her mother mistreated the father who was an alcoholic. The patient was afraid of her mother and never got along with her, but felt guilty about this. She was high strung, dependent, and subject to tantrums of temper. Sexual relations were unsatisfactory. She was helped by psychotherapy.

Case 9 was that of an unmarried school teacher of thirty-one who fell ill after her first menstruation. Her father was quiet and reserved and the mother was talkative, overly protective and the ruler of the household. The patient had always been shy and quiet. She never mixed with people and it was hard for her to become acquainted. She never had a beau. She was depressed with each period. She showed a rather silly attitude toward her troubles, but eventually was helped by psychotherapy and narco-analysis. Under analysis she showed much hostility to her mother.

Case 10 was that of a married woman of twenty-seven who had been ill since the birth of a child. The mother was very strict and austere. The patient's sex interests were limited, and she was never much interested in boys. She had much psychotherapy but did not develop much insight.

In practically all of these cases one finds the story of a somewhat psychopathic sex-hating, reserved or submissive woman held under the thumb of a domineering mother. In all cases menstruation was irregular, difficult and painful. All of the women had an asthenic build. Many had an abnormal distribution of body hair. The father was usually nervous, ineffectual and dominated by the mother. All of the patients had a normal intellectual capacity with intelligence quotients between 90 and 114 with a mean of 103, but adjustment to life was unsatisfactory. They were hypersensitive; they tended to worry, they had many fears and they easily became upset and discouraged.

The scores on the Bell adjustment inventory indicated average home adjustment, a very unsatisfactory health adjustment, a marked tendency to be socially retiring, and a very unsatisfactory emotional adjustment. All of the patients suffered from anorexia, constant fatigue, loss of weight, gastro-intestinal symptoms and insomnia. They did not like to participate in group activities. They were emotionally unstable and easily disturbed by criticism. They worried over every possible misfortune. Their feelings were easily hurt. They felt miserable, with groundless fears, and they cried easily. They felt lonely even when with people.

The total picture then is that of an immature and somewhat colorless personality with the inner life poorly integrated. Thinking is superficial and unimaginative. These patients stopped growing mentally at the age of puberty.

Insulin shocks given to five of the patients resulted in a gain of weight and appetite. They ate normally again. The authors doubted that anorexia is an incipient and mild form of schizophrenia. Insulin shock may help but it must be followed up by strong psychotherapy if results are to be lasting.

Hostility to the domineering mother seems often to be the most important factor in producing the situation. When put under amyntal, these patients showed this great hostility even when, on the surface, they seemed dependent and loving. In the case of most of these patients, the girl not only had to live unhappily with the psychopathic mother but she had to carry in her body and brain the bad inheritance derived from her abnormal parents. It would appear that a gastroenterologist would do well always to get the help of a psychiatrist before attempting treatment of a patient with severe anorexia nervosa. In many cases in which the patient refuses to co-operate or to gain insight, or in which the home situation is bad and cannot be changed, the physician had better not waste his time on extended treatment.

W. C. A.

COMMENT

THE VIRUS OF LYMPHOGRANULOMA VENEREUM

The gastroenterologist must always be interested in lymphogranuloma venereum because occasionally he sees patients with lesions in or about the rectum which may be due to this strange disease. Today it is known that it is fairly common in persons who are sexually promiscuous especially in the Southern States and the countries below the Rio Grande.

There is a good review of knowledge in regard to the virus of this disease in the June, 1945, number of the "Annals of Internal Medicine." The virus appears to be from 0.125 to 0.175 micron in diameter and it can now be grown on the allantochorionic membrane of the embryo chick. It is neutralized by the serum of infected persons and a complement fixation test has been worked out.

Interestingly, the virus appears to be related to that of psittacosis, trachoma, inclusion blennorrhea and meningopneumonitis of Francis and Magill. It is unusual in that it is to some degree susceptible to the sulfonamide drugs.

It is not yet known what the status is of all those persons without obvious lesions who react positively to the Frei antigen. It seems probable that many are carrying the disease in latent form.

For an excellent review of the whole subject of lymphogranuloma venereum the reader can consult Herbert Koteen's article in Medicine (24:1-69 [Feb.] 1945). His conclusions are based on personal observations and a bibliography of 369 titles.

According to Koteen the first symptom of proctitis due to lymphogranuloma venereum is rectal bleeding with purulent discharge. The mucosa becomes inflamed and hyperemic with localized denuded areas and places covered with granulation tissue.

If treatment is well carried out in this stage, complete healing can be expected but if treatment is delayed, scar tissue will form. Curiously, in Baltimore, rectal stricture due to this cause is found almost exclusively in colored women. In them the inflammation may perhaps work through from lesions in the vagina.

Following the development of a rectal stricture, with the shutting off of lymph channels, little tumors called "lymphorrhoids" may form. Only by histologic study can these little masses be distinguished from malignant tumors.

Cases have been described in which the primary lesion of this disease appeared in the mouth or on the lips.

Many attempts made to isolate the virus from tissues involved in terminal

ileitis have failed, and all the patients with this disease tested with the Frei antigen have failed to react. After discussing the work of Goodman, Paulson, Palmer and his colleagues, and Weber and Bargen, Koteen concluded that there is little evidence to support the view that chronic ulcerative colitis is often due to the virus of lymphogranuloma venereum. Most of the patients tested had a negative Frei test.

W. C. A.

A DRUG WHICH DOUBLES THE ANALGESIC EFFECTS OF OPIUM AND ITS DERIVATIVES

At the last meeting of the Society for Pharmacology and Experimental Therapeutics Donald Slaughter reported that in men and women, neostigmine greatly enhances the analgesic action of the usual therapeutic doses of opium and its derivatives. This was determined with the help of the Wolff, Hardy and Goodell apparatus for determining the threshold for pain of the individual.

Neostigmine, when injected subcutaneously in doses of 0.5 mg. together with pantopon, morphine, or dilaudid about doubled the effect of the analgesic. When given with codeine it more than doubled the effect of the drug.

Certainly this interesting observation should immediately be checked in all pharmacologic laboratories. If it should work out in clinical practice as well as it has in the research laboratory, Dr. Slaughter's discovery will represent one of the big advances made in the relief of human suffering.

W. C. A.

BOOK REVIEWS

PREVENTIVE MEDICINE AND PUBLIC HEALTH. *By Wilson G. Smillie.* The Macmillan Company. 1946. 607 pp.

This book was prepared not for health officers, epidemiologists, sanitary engineers or others who engage in public health work as a career; it was prepared for medical students who are expecting to practice clinical medicine, and who are interested primarily in the diagnosis and treatment of disease. The major thesis of this text is that the practicing physician has an obligation to prevent illness in his patients and in the community, and to promote health in the family and in the city. Section 1 is on population trends, public health, and vital statistics. Section 2 is on environmental sanitation. Section 3 is on the control of communicable diseases. Section 4 is on child hygiene. Section 5 is on adult health protection and promotion. Section 6 is on public health administration.

The author is Professor of Public Health and Preventive Medicine in Cornell. Not only physicians but intelligent laymen will be interested in reading this volume.

MEDICAL BIOCHEMISTRY. *By Mark R. Everett.* Second edition. Paul B. Hoeber, New York. 1946. 767 pp. Price \$7.00.

This is a learned and very useful book, crammed as it is with information. It represents years of reading and studying and writing. It is full of tables and graphic formulas. It should be a good text for college courses.

CHEMISTRY OF FOOD NUTRITION. *By Henry C. Sherman, Ph.D., Sc.D.* Seventh Edition. The Macmillan Company, New York. 1946. pp. 675. Price \$3.75.

In order thoroughly to incorporate all recent advances in dietetics, every chapter has been revised, several have been rewritten, and two new chapters on the nutritional characteristics of the chief groups of foods and on the causes and extent of variations in the nutritive values of food have been added. The text is interesting and authoritative, and fine bibliographies are appended to the several chapters. The book can be highly recommended. The fact that it is in its seventh edition shows how well it has been received by everyone.

MEN WITHOUT GUNS. *By DeWitt Mackenzie.* The Blakiston Company, Philadelphia. 1945. 47 pp. Illustrated with 137 Plates.

This is a remarkable book of great historical interest. It is made up of pictures showing the medical service during the war. Most of these pictures are reproductions of vivid paintings. They show medicine as it was practiced at the front, under battle conditions, on the beaches, in the jungles, in improvised hospitals and in the Base hospitals.

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MOUTH AND ESOPHAGUS

MCKAY, J. W. The radiological diagnosis of certain diseases of the lower esophagus. *Surg. Clinics N. Am.*, 306 (Apr.) 1946. Thoracic pain may be due not only to heart disease but to esophageal disease as well. The technic of radiologic examination of the esophagus is important. The Valsalva test is of value in demonstrating the phrenic ampulla and esophageal varices. The commonest error is in mistaking the phrenic ampulla for an esophageal hiatus hernia. Familiarity with the normal anatomy and physiology of the esophagus will facilitate the interpretation of radiological findings. In cases without evidence of heart disease and with precordial or substernal pain, a fluoroscopic examination of the esophagus should be done in a search for esophago-spasm.

FRANK G. VAL DEZ.

HERMAN, M., AND SINGER, E. Paracardiac esophageal hiatal hernia. *N. Y. State J. Med.*, 46: 1020 (May) 1946. This report concerns a case of para-eso-

phageal hiatus hernia in a 53 year old male, who had had gastric symptoms for 34 years. Acute symptoms developed one day simulating coronary thrombosis. X-ray studies of the gastro-intestinal tract revealed the true nature of the condition. Pneumoperitoneum was instituted in an attempt to reduce the hernia, but without success.

PHILIP LEVITSKY.

STOMACH

LAWRENCE, E. A., AND KAY, J. H. Carcinoma of the stomach. A ten-year survey made in a general hospital. *Surgery*, 19: 504 (Apr.) 1946.

The authors reviewed 208 patients with carcinoma of the stomach, treated at the New Haven Hospital in the years 1931 to 1940 inclusive. Follow-up was obtained in 207 of these patients. The age and sex distribution was similar to those reported in other series. Of the 208 patients, 82 were found to be inoperable or refused operation, 57 had only exploration, and 21 had palliative operations. Radical gastrec-

tomy was performed in 48 (23% of the total). In some instances, radical gastrectomy was performed even though it was noted at the time of operation that metastases had already formed. Of the 48 subjected to radical gastrectomy, 30 survived the operation.

Of those patients who survived operation, 13 survived for three years, and 9 survived for five years. This represents, therefore, a 5-year survival rate of 4.3% of the total 208 patients, an 18.7% survival rate of those who had had radical surgery, and a 30% survival rate of those who survived this surgery. It was emphasized that the great losses in carcinoma of the stomach are due to inoperability, unresectability, and resection mortality. It therefore becomes necessary to direct educational efforts along lines which will emphasize the importance of operating upon a patient before the tumor becomes unresectable. If the patient can survive radical resection, there is 1 chance in 3 that he will survive 5 years.

HENRY TUMEN.

RICKLES, J. A. Multiple carcinomas of the stomach—case presentation with five primary separate malignant lesions treated by total transthoracic gastrectomy. *Surgery*, 19: 229 (Feb.) 1946. The author reports in detail a patient with 5 primary carcinomas of the stomach treated by transthoracic total gastrectomy. He believes that this is the first reported case of this type. The immediate post-operative course was satisfactory but the patient died 3 months following operation, possibly as a result of metastases.

HENRY TUMEN.

FICARRA, B. J. Hyperuricemia in gastric cancer. *Surgery*, 19: 223 (Feb.) 1946.

In a previous paper the author has called attention to the fact that it is possible to differentiate hypoproteinemia secondary to insufficient dietary protein from hypoproteinemia secondary to accelerated endogenous protein depletion, by the fact that in the case of the latter there is an elevation of the blood uric acid. This is thought to result from the patient's attempt to replenish his protein deficiency by utilizing pro-

tein secured by breaking down his own cells. Hyperuricemia is an indicator of the degree of endogenous protein metabolic activity.

Comparison of the serum protein and blood uric acid levels with the clinical status of the patient is said to indicate that high uric acid and low blood protein levels are found most often in patients who have had a markedly deficient intake and have, therefore, been forced to call upon their own body protein to rectify the hypoproteinemia. It was concluded that most complications occurred in patients with gastric carcinoma who have marked hyperuricemia. These complications included weakness and fatigability, nutritional edema, lowered resistance to infection, and post-operative gouty arthritis. The author concluded that a more complete evaluation of the nutritional state of the surgical patient can be obtained by studying the blood uric acid in conjunction with the serum protein.

HENRY TUMEN.

KIERNAN, P. C. and LARSON, R. Small ulcerating lesions of the stomach: report of two cases. *Proc. Staff Meet. Mayo Clinic*, 21: 218 (May) 1946.

Ten per cent of ulcerating lesions of the lesser curvature of the stomach prove to be malignant upon microscopic examination; 40% of those in the prepyloric area, and 96% of those on the greater curvature are malignant. The risk of laparotomy and gastric resection is far less than the danger of permitting a malignant gastric lesion to go by on the assumption that it is benign. This presentation stresses the advisability of surgical exploration as the treatment of choice in gastric ulcer.

Two cases operated upon the same day are given. In one case, a penetrating lesion was present high up on the lesser curvature, and as frozen section revealed a benign lesion, simple excision was done. The second case had a typical ulcer history of two years duration, and X-ray examination demonstrated a small ulcer at the angle on the lesser curvature. Subtotal resection was performed and the pathologist reported an adenocarcinoma, grade three. It is emphasized that the danger of a gastric lesion's being malignant is a very real one, and

avoidance of procrastination with medical treatment is recommended in any case with doubtful response. The larger the lesion, the more surely should it be considered malignant.

FRANK NEUWELT.

BOWEL

BLACK, B. M. AND EVERETT, J. A. Peritonitis following malignant obstruction of sigmoid and free perforation: Report of three cases. *Proc. Staff Meet. Mayo Clinic*, 21: 137 (Apr.) 1946.

Sudden perforation of the bowel with generalized peritonitis is an unusual and grave complication of carcinoma of the colon, and complete obstruction of the colon is found generally in such instances. The presence of an efficient ileocecal sphincter results in a closed-loop obstruction with consequent distension, ischemia, infarction of the bowel, and tears in the bowel wall, particularly of the easily distensible cecum. Also, as the ileocecal valve seals off the obstructed area, vomiting may be a late symptom and intestinal intubation may be of little value in relief of the distension.

Three case reports are presented of carcinoma of the colon with obstruction and subsequent perforation; in fact, the perforation occurred in the third case after the patient had been admitted to the hospital. In each of these cases, the perforation occurred near the site of the malignant lesion. The importance of doing a double-barreled colostomy above the area of perforation, in order to divert the fecal stream entirely, is emphasized. At subsequent celiotomy resection of the cancer was performed and any necessary plastic repairs done. Chemotherapy has undoubtedly contributed much to the successful outcome of such cases.

FRANK NEUWELT.

FRYFOGLE, J. D., KIERNAN, P. C. AND DOCKERTY, M. B. Lymphoblastoma of the small intestine: Report of case. *Proc. Staff Meet. Mayo Clinic*, 21: 161 (Apr.) 1946.

Mention of lymphoblastoma brings to mind thoughts of large masses of lymph glands, enlarged spleen, abdominal masses, etc.

The 21 cases of lymphoblastoma reported herein are of particular interest because they did not originate in large glandular masses but in the single small follicles of the small bowel. Such follicles are plentiful in the ileum, fewer in the jejunum, and almost non-existent in the duodenum. Approximately 1% of malignant tumors of the gastro-intestinal tract are lymphoblastomas. The 20 previous cases were classified as follows: 12 instances of small round cell lymphoblastoma, 2 of the large round cell variety, 4 instances of Hodgkin's disease, and 2 considered as lymphosarcoma. The lesions were situated in the ileum in 9 cases, in the jejunum in 10, and in the duodenum in 1. At operation, multiple lesions were noted in 9 cases, and lymph nodes were involved in 18 of these 20 cases.

The presenting symptoms for the most part were vague as to location and severity. The chief complaints were as follows: abdominal pain in 6, low grade abdominal obstruction in 5, weakness and loss of weight in 2, and appendicitis in 3. In case of obstruction, the fecal stream is not stopped by the growth of a fibrous napkin ring about the bowel, but the tumor destroys the peristaltic motion of the bowel by involvement of the submucosal nerve plexus causing a condition which simulates real obstruction. A seven year old child had had low grade stomach aches for 5 weeks.

The child developed symptoms of obstruction while under observation, and at laparotomy a small egg sized lymphoblastoma of the small round cell type was resected. The child was given radiation therapy post-operatively, but had multiple metastases 4 months later. Lymphoblastoma carries a very grave prognosis, even though the whole lesion may be resected and radiation therapy is employed. Nevertheless, in case of extensive involvement of stomach or cecum, radical resection plus radiation may result in clinical cure.

FRANK NEUWELT.

KEYES, E. L. AND COOK, M. M. Diagnosis of acute appendicitis in the presence of diarrhea. *Arch. Surg.*, 52: 429 (Apr.) 1946.

A careful analysis of the early history helps

to differentiate acute appendicitis from enteritis. A proper evaluation of the bowel urge, diarrhea, and nausea has proven to be the greatest aid to the authors in determining the early stage of appendicitis.

In acute appendicitis the early pain is persistent, while in enteritis it is intermittent. The bowel urge associated with acute appendicitis persists despite diarrhea, defecation, or the passage of gas; in enteritis bowel urge is completely, if temporarily, relieved by defecation or diarrhea. Diarrhea and nausea are subordinate to the bowel urge in appendicitis while they usually dominate the clinical picture in enteritis.

During the later stage of localisation tenderness increasing near McBurney's point is more common in acute appendicitis than in enteritis. Likewise, muscle spasm, rebound, and rectal tenderness and other signs of peritoneal irritation occur commonly in acute appendicitis and rarely in enteritis.

C. WILMER WIRTS, JR.

HUNT, C. J. Early diagnosis and management of small intestinal obstruction. *Surgery*, 19: 237 (Feb.) 1946.

This is a general discussion of the problems involved in the early diagnosis and management of small intestinal obstruction. The most important feature of the paper is the emphasis on the use of the Miller-Abbott tube in those patients who have simple adhesive obstructions with extensive proximal dilatation. It is also emphasized that use of the tube is contra-indicated as a pre-operative measure in loop obstruction, volvulus, or in strangulated obstruction when viability of the bowel is in jeopardy.

Mention is made of the surgical treatment during the past five years of 41 patients with small bowel obstruction and of the treatment of several others in whom recovery took place without operation. In 29 patients with small bowel obstruction, no resection was necessary. In 10 instances it was necessary to perform resections of devitalized bowel.

HENRY TUMEN.

BORLAND, J. L. Treatment of some common infections of the bowel with sulfonamide drugs. *Southern Med. J.*, 39: 285 (Apr.) 1946.

This presentation is a summary of the observations of a medical officer, stationed with a general hospital in the Southwest Pacific, regarding the treatment of infectious diseases of the intestinal tract with sulfonamide compounds. In bacillary dysentery, sulfadiazine and sulfathiazole were tried in the usual recommended dosage of 2 to 4 g. initial dose followed by 2 g. every 4 hours for periods up to one week.

In general the results were better in all cases and curative in most. However, a certain percentage of acute and chronic cases did not respond at all or relapsed at the cessation of the drug. The majority of "carriers" were not affected. In cases comparable as to severity, duration, proctologic appearance, and infecting organism, the "failures" occurred when the blood level was low or when the duration of therapy was short. On the basis of the reaction to sulfonamides, the conclusion was reached that asymptomatic cases with positive stool cultures were not true carriers but had chronic infection of the bowel wall with lesions not detectable by present methods. The second great group of cases which constituted a problem were the ulcerative colitis cases. There were no severe acute ulcerative colitis cases or cases with advanced destruction of the bowel. Improvement in the local appearance of the bowel followed the use of sulfonamides. There was a blood level of 14-16. Relapse occurred within 2-4 weeks after therapy ceased. There was no appreciable effect in several patients with salmonella infections who had received adequate sulfonamide therapy. High sulfonamide levels were maintained for a period of at least 3 weeks in over 50 patients who had infections of the bowel. No toxic reaction was observed. The urine was kept alkaline at all times and an output of at least 2,000 cc. in 24 hours was insisted upon.

IRVING GRAY.

LIVER AND GALL-BLADDER

GAD, I. Investigations of the phosphatase activity in serum and organs after ligation of the common bile duct in dogs. *Acta Physiol. Scand.*, 11: 151 (Apr.) 1946.

It has long been known that obstructive jaundice, both in man and in experimental animals, is accompanied by an increase in the serum phosphatase activity. Bodansky has stated that the increase in serum phosphatase activity is due to an increased delivery of phosphatase from the liver tissue. This explanation appears to be the most probable one of all the advanced hypotheses. Since, however, the phosphatase content of the liver under normal conditions is not very high, a study of the phosphatase activity of the liver under icteric conditions was necessary in order to decide whether this hypothesis can be regarded as well founded.

The present paper deals with the changes in the phosphatase content of the liver and other organs and the serum, which arise from a ligation of the common bile duct in dogs. Following this procedure, there is an increase in serum phosphatase activity, a phenomenon which was known earlier, but produces simultaneously an increase in the phosphatase content of liver and intestinal tissues. Some interdependence seems to exist between the phosphatase activity in serum and in these organs during obstructive jaundice. There is no parallelism seen between the intensity of the jaundice and serum phosphatase activity. It is probable that the increased serum phosphatase during obstructive jaundice originates from the intestine which, both normally and under icteric conditions, may give off its phosphatase to the liver, functioning as a kind of regulator for the phosphatase of the plasma. On the basis of the procedures of Bodansky and other investigators, an analytical method is described for the determination of the phosphatase activity in serum and organ extracts. Finally, it is assumed that the increased serum phosphatase during obstructive jaundice may originate from the intestine.

ALBERT CORNELL.

MILLER, D. Papilloma of the gall bladder. *New Eng. J. Med.*, 234: 473 (Apr.) 1946.

The author reports three cases of papilloma of the gall bladder in which the pre-operative diagnosis was correctly made in each instance by the roentgenologist. Diagnosis was confirmed by operation and histological study of the gall bladder. All three patients—a 36 year old woman, a 46 year old man, and a 35 year old man—all had digestive symptoms referred to the upper abdomen. The clinical symptoms were suggestive of gall bladder disease. The author believes that when papilloma gives rise to symptoms, the treatment should be surgical (cholecystectomy). Papillomas of the gall bladder are infrequent and are rarely associated with carcinoma. They may give rise to symptoms similar to those of chronic cholecystitis, and can be diagnosed pre-operatively by roentgen-ray examination.

IRVING GRAY.

MORRISON, L. M. The response of cirrhosis of the liver to an intensive combined therapy. *Ann. Int. Med.*, 24: 465 (Mar.) 1946.

Sixty-two patients with cirrhosis of the liver, or chronic hepatitis, were divided into 3 groups, each treated for 2 years over an 8-year period of time. The control group (23 patients) was treated by older methods: a high carbohydrate diet (i.v. glucose) and, where ascites existed, use of mercurial diuretics, ammonium chloride, paracentesis, and other palliatives. The second group (19 patients) was treated by a modified Patek's regime, consisting of a moderate protein-carbohydrate, low fat diet—supplemented orally by 25 g. of Brewer's yeast daily, and parenterally by the injection of 10 mg. each of thiamine chloride and niacinamide daily, 0.3 mg. riboflavin every other day, and 3-5 cc. of whole liver extract every other day. The third group (20 patients) was treated with the "intensive combined" plan of treatment, consisting of maximum protein (200-300 g.), high carbohydrate (300-500 g.), high vitamin, low fat (50-100 g.), and 2500-4000 calories. A whole unfractionated liver extract (3-5 cc.) was given daily for 10 days,

then every other day for 10 days, then 2-3 times weekly. This was reinforced with 10 mg. of vitamin B, 0.3 mg. of riboflavin, and 10 mg. nicotinamide in each injection of liver. In addition, oral vitamin supplements were added, 2 g. each of methionine and choline in capsule form being given daily. Casein and cystine were assured by high intake of skimmed milk and cottage cheese daily.

Results showed that with this newer therapy there was a sharp reduction in the length of disability, from 82% to 28% in those without ascites, and from 83% to 66% in those with ascites. Mortality dropped from 27% in the control group to 0 in the intensive combined therapy group without ascites, and from 75% to 11% in those with ascites.

FRANK G. VAL DEZ.

BEAVEN, T. E. D., AND DUNCAN, G. W.
Congenital atresia of the common bile duct. Report of a successful case. Brit. J. Surg., 33: 378 (Apr.) 1946.

Congenital anomalies of the bile passage are frequently associated with those of other organs. The outstanding symptom of congenital atresia of the common bile duct is a progressive deep jaundice. The condition must be differentiated from icterus gravis neonatorum (which appears earlier, and shows erythroblastic changes and possible disturbed Rh factors), from congenital syphilis (which presents a milder jaundice, hemorrhages, a rash, and enlargement of the liver and spleen), from alcoholic jaundice (which is milder and accompanied by an anemia with increased fragility), from physiological jaundice (which is transient and mild), and from jaundice and infective hepatitis (which are quite rare). Once the diagnosis is established and the child properly prepared, immediate surgery is indicated to prevent severe liver damage.

In the case reported, a successful cholecystogastrostomy was done with satisfactory recovery, except for a pyelitis which suggested the possibility of an anomaly of the urinary tract.

J. DUFFY HANCOCK.

BULLARD, R. W., JR. Alkaline phosphatase and metastatic liver disease. *Surgery*, 19: 379 (Mar.) 1946.

This paper includes a brief resume of knowledge concerning the formation and metabolism of alkaline phosphatase. The alkaline phosphatase level was studied in 85 patients with carcinoma and in 26 controls. The King-Armstrong method was employed and 12 units was considered the upper limit of normal. In the 85 patients with carcinoma, elevation of the alkaline phosphatase was found to indicate metastatic involvement of the liver, if the presence of certain other disease such as cirrhosis, obstructive jaundice, or bone disease was ruled out. There were 15 such cases, although one of these patients had jaundice with the metastases. In 6 additional patients, however, there was definite, sometimes marked, liver involvement with normal phosphatase levels. There were 4 additional patients with questionable single small liver nodules and normal phosphatase. It was therefore concluded that the presence of a high phosphatase in patients with malignancy is diagnostic of liver metastases if obstructive jaundice, cirrhosis, or bony involvement are not also present. A normal phosphatase, however, does not rule out the presence of liver metastases.

HENRY TUMEN.

CAMPBELL, J. A., AND TAGNON, H. J.
The intravenous glucose-tolerance test in liver disease. *New Eng. J. Med.*, 234: 216 (Feb.) 1946.

The 25 cases from which the data in this report were obtained were studied as they appeared on the wards of the Boston City Hospital, with no attempt either to include or to exclude patients with diabetic tendencies. The only criterion for selection was clinical and laboratory evidence of marked liver damage at the time the glucose-tolerance tests were performed. Of the 25 patients studied, 15 gave histories of markedly elevated alcoholic intake, 8 were moderate drinkers, and 2 denied any use of alcoholic beverages. Thirteen patients gave dietary histories of food intake adequate in vitamin content as well as in caloric value. The general nutritional status of these patients

at the time the tests were performed was judged to be good in 11 cases, fair in 4, and poor in 10. No patient, however, showed either marked obesity or emaciation. Included in the cases with moderate depression in the blood-sugar concentration are 3 of cirrhosis of the portal type, and the single case of biliary cirrhosis in the series. By far the greatest portion of the cases with liver disease, however, were in the group showing normal blood-sugar values, both in the fasting state and 2 hours after the test glucose injection. In the present study, the patients exhibited glycosuria during the test in all cases except two. The maximum total urinary glucose excreted in any one case was 2.50 g., with an average total of 0.67 g., showing no appreciable deviation from the normal. The advantages of the intravenous as compared with the oral glucose-tolerance test are manifold. Although extreme variations appeared in individual tests, by far the greater proportion of the values obtained were within normal range. No diagnostic value could be assigned to the tests in this series as an index either to liver function or to disturbed carbohydrate metabolism.

IRVING GRAY.

THORN, G. W., ARMSTRONG, S. H., JR., AND DAVENPORT, V. D. Chemical, clinical, and immunological studies on the products of human plasma fractionation. XXXI. The use of salt-poor concentrated human serum albumin solution in the treatment of hepatic cirrhosis. *J. Clin. Invest.*, 25: 304 (May) 1946.

Five subjects with hepatic cirrhosis resulting in hypoalbuminemia, edema, and ascites were given a diet containing at least 1 g. of protein per kg. body weight, over 200 g. of carbohydrate, and 30-70 g. of fat daily. The diet was salt poor (1-2 g. of salt daily), except in one patient. A constant quantity of vitamin B complex and liver extract was given. Intake of fluids was maintained constantly. Salt poor albumin, in the form of a specially prepared 25% solution, diluted to a 10% concentration, with sterile 6% dextrose solution, was used. This was administered intravenously at the rate of

approximately 100 ml. per hour, in a standard daily dosage of 50 g. of albumin.

In the presence of generalized edema, striking increase in the urine volume was obtained, but the weight loss was less than was expected. Without edema, but with ascites, this increase in urine output was not attained. Increase in serum albumin levels, proportionate to the dosage, were obtained. These levels were reached and sustained in cirrhotic patients in a much more striking manner than in nephrotic patients, the former retaining an average of 20% more of the administered protein than did the latter.

Little or none of the albumin administered intravenously was excreted in the urine. Approximately 80% of the albumin was retained when 50 to 150 g. were administered; with larger doses, approximately 50% was retained. In contrast to the effectiveness of albumin administered intravenously in raising the serum albumin level and increasing positive nitrogen balance, oral administration was ineffective.

SAM OVERSTREET.

PANCREAS

HOLT, J. F. The roentgen diagnosis of pancreatic cyst. *Radiol.*, 36: 329 (Apr.) 1946.

The symptoms of pancreatic cyst are not at all distinctive and may be closely simulated by numerous other intra-abdominal lesions. Certainly the most constant and important subjective complaint is pain, but it is so variable in location and extent that it has but little diagnostic value. Loss of weight, weakness, nausea, vomiting, and diarrhea are common but even less consistent symptoms. Jaundice may occur when a cyst grows large enough to obstruct the biliary duct system.

If the cyst is large enough to produce symptoms, a smoothly rounded mass may usually be palpated in the upper portion of the abdomen. During the roentgenological examination, the importance of anterior displacement of the stomach and smoothly rounded indentation relatively high on the greater gastric curvature as a combination of roentgen signs suggestive of cyst in the tail of the pancreas should be clearly appre-

ciated. This is especially true when such deformity is encountered in conjunction with a rounded, ballotable, freely movable mass in the left upper quadrant of the abdomen.

Conceivably, an enlarged spleen, splenic cyst, mesenteric cyst, omental cyst, or retroperitoneal neoplasm might very well produce a similar localized indentation of the mid-portion of the greater gastric curvature, but such has not been our experience. Under such circumstances, the roentgenologist not only can make a diagnosis of pancreatic cyst with reasonable assurance of being correct, but he can be of further assistance to the surgeon by suggesting the exact site of origin of the lesion.

FRANZ J. LUST.

ANEMIAS

HADEN, R. L., The treatment of pernicious anemia. *Cleveland Clinic Quart.*, 13: 43 (Apr.) 1946.

Achlorhydria and macrocytosis of the red cells are the two constant findings in untreated pernicious anemia. Cell size is the most important criterion of complete therapy. The deficiency in idiopathic pernicious anemia is permanent, so treatment is required throughout the life of the patient. The schedule of therapy used by the author consists of the following: first 2 weeks, daily injections of 15 units (1 cc.) of a potent liver extract; next 3-month period, 15 units twice weekly; next 3-month period, 15 units weekly; remainder of the patient's life, 15 units monthly.

The neurologic lesions never advance and usually improve, often to a striking degree, with this regime. The gastro-intestinal symptoms are relieved entirely although the achlorhydria is uninfluenced. During infections, more extract should be given. Iron, hydrochloric acid, and other medication are seldom needed. A complete diet should be insisted upon.

FRANK G. VAL DEZ.

EVANS, R. S. Chronic hemolytic anemia—observations on the effect of fat content of the diet and multiple red cell transfusions. *Arch. Int. Med.*, 77: 544 (May 1946).

The histories of two patients with chronic hemolytic anemia are presented. One always exhibited spherocytosis and an increased fragility of the red blood cells in hypotonic saline solution. The onset of the hemolytic anemia followed the therapeutic injection of colloidal gold for arthritis. No hemolytic agent could be demonstrated in vitro. However, within 24 to 48 hours after massive transfusions of red blood cells, quantitative fragility curves (which immediately after transfusion had temporarily shifted towards a normal range) showed again increased fragility. This suggested that the transfused erythrocytes had become increasingly fragile. These changes were accompanied by an increase in the figures for mean cell volume and a decrease in those for mean cell diameter (i.e. spherocytosis). Evans thinks that a lytic substance produced these changes by damaging the cell wall with resultant absorption of fluid.

The second patient never exhibited spherocytosis or increased fragility. Restoration of the circulating hemoglobin to a normal level by multiple transfusions of red blood cells was followed by evidence of diminished hemolysis. Evans suggests that the reticulocytes or newly formed cells were the ones most susceptible to hemolysis in this patient and that the lessened hemolysis was caused by the lessened need for new blood formation after transfusion.

Studies made on the pigment content of blood and feces in both patients after high and low fat diets failed to give any information suggesting that the fat content of the diet was of therapeutic importance in the rate of blood destruction.

EDGAR WAYBURN.

ULCER

MIRALDT-KRETCHMAR, M. Recrudescence des ulcères gastro-duodénaux au cours des années 1939-1944 et alimentation en période de guerre. (Recrudescence of Gastroduodenal Ulcer and Alimentation During the War Period.) *Gastroenterologia*, 70: 225 (1945).

A review of the literature reveals evidence of an increase in the incidence of peptic ulcer in Switzerland during World War II. There was relatively a greater number of

cases of gastric than of duodenal ulcer. The incidence of gastritis and of carcinoma of the stomach was not significantly altered. The larger number of ulcer cases observed during the war period is attributable both to an increase of recurrences of the disease and a greater number of new cases. During this time the diet was modified, consisting of large amounts of vegetables and foods containing cellulose, with a reduction in the amount of milk, eggs and butter. Careful questioning of patients with ulcer revealed that they usually attributed the recurrence of symptoms to this change of diet.

CHARLES A. FLOOD.

GARBAT, A. L. Problems of peptic ulcer in the armed forces and in the returned soldiers. *N. Y. State J. Med.*, 46: 894 (Apr.) 1946.

Approximately 10% of all medical hospital admissions in the armed forces are gastrointestinal cases, and of these 10% are due to ulcer. Battle action was not necessarily the cause, since high instances are present among non-combat troops; also, in many cases, symptoms first appeared after the men had been removed to rest areas. Contributing causes to the high incidence of peptic ulcer are the changed emotional status, army diet, abuse of coffee, alcohol, and tobacco. The rate of recurrence remained high as long as the cases were kept in the services, even though in a limited capacity. On discharge, the rate of recurrence depends on the veterans readjustment to civilian and domestic life.

The great majority of emotionally unstable ulcer patients should be treated by the medical man by conventional methods, and do not require major psychotherapy. To prevent recurrence, a proper bland diet sufficient in calories and vitamins takes first place. Excessive fatigue should be avoided as well as emotional upsets and chronic annoyances. Antacids, antispasmodics, and nerve sedatives should be used liberally. Most cases are satisfactorily treated in ambulatory manner; some may even take up light employment. Certain cases require bed rest, such as those with acute hemorrhage or persistent oozing, deep penetrating ulcers with excessive pain,

complications of surgery, and those with intractable ulcers.

The one complication requiring immediate operation is acute perforation. In the ex-service man under 50, repeated hemorrhage is not necessarily an indication for surgery. Pyloric obstruction due to cicatrization, and intractable ulcer are often considered surgical indications. An ulcer attack is considered arrested when the sense of discomfort is gone, there is no longer X-ray evidence of irritability or spasm, occult bleeding is absent, hyperacidity diminished and—in the case of gastric ulcer—gastroscopic evidence of healing.

PHILIP LEVITSKY.

HINTON, J. W. The surgical treatment of chronic duodenal ulcer. *Bull. N. Y. Acad. Med.*, 22: 227 (May) 1946.

The value of surgery as the procedure of choice in the therapy of chronic duodenal ulcer is dependent upon the result of previous medical management. Analysis has shown that surgical failures are often due to inadequate pre-operative medical care, or occur when surgery is used as a short cut to restoring the patient's earning capacity. Observations over the past 18 years have shown that chronic duodenal ulcer can be treated most satisfactorily on a medical regime. Of 1256 peptic ulcers, 89% were duodenal. Over a 14 year period, there were 993 unoperated cases, and in only 14% of these had operation been advised. During 1942 and 1943, 85 operations were reported, of which 19 (22%) had been surgical failures from a previous operation.

It seems apparent that through an appreciation of the value of prolonged medical treatment a high percentage of surgical failures can be avoided. The indications for surgery frequently discussed in the literature are pyloric stenosis, recurrent hemorrhage, penetrating ulcers, lack of cooperation, and intractable pain. In the author's opinion, only the last mentioned condition is the one real indication for surgical intervention. A patient with a stenosing or obstructing ulcer can be relieved by medical management unless he has severe pain. In the past 13 years, no patient with so-called pyloric obstruction unaccompanied by severe pain

has been referred for surgical therapy. Many have been advised against operation. A patient with a massive hemorrhage who is not suffering pain seldom, if ever, requires operative intervention as an elective procedure. Patients who will not cooperate under medical management should not be operated upon. If the surgeon accepts this type of patient for operation, the results will be unsatisfactory. Patients who can be helped by gastroenterostomy can usually be helped by a prolonged medical regimen. Patients who do not have the duodenal ulcer removed have more complaints than those in whom it is removed. The end-results seem to justify the insistence on removal of the adherent ulcer in toto. Chronic inflammatory processes, when surgically treated, require removal and the adherent duodenal ulcer is not an exception.

ALBERT CORNELL.

GORDON-TAYLOR, G. The present position of surgery in the treatment of bleeding peptic ulcer. *Brit. J. Surg.*, 33: 336 (Apr.) 1946.

For the successful management of these cases, a well organized service with close cooperation between internists and surgeons, is advocated. Strict standardization of treatment is undesirable. Every case should be regarded as a special problem deserving of the most careful attention. The mortality of exclusive non-surgical management has been drastically reduced by early feeding, prevention of dehydration, and the use of "drip" transfusion—the latter being emphasized as most important also in the cases treated surgically. However, early surgical treatment probably is the safer plan.

Immediate operation is indicated where terrific hemorrhage suggests that some large vessel has been eroded. Urgent surgery should be resorted to in patients over 50 with definite chronic ulcers, when the radial arteries are thickened and tortuous, where there is concomitant hemorrhage and perforation, when hemorrhage is recurrent, and where severe pain is a prominent factor whether it precede or follow the hemorrhage.

Local regional anesthesia is recommended. The Judin operation is described and illustrated. This procedure converts the incised

first portion of the duodenum into a cone and then a snail-like form which serves as a tampon when sutured to the ulcer base penetrating into the head of the pancreas.

J. DUFFY HANCOCK.

PROCTOLOGY

SKIR, I. Proctoscopy and barium colon study in the diagnosis of rectal conditions. *N. Y. State J. Med.*, 46: 1017 (May) 1946.

The author advises that in all rectal conditions, digital and proctosigmoidoscopic examination precede barium enema, in order to save time, and to avoid a false sense of security that a negative barium enema imparts. A barium enema frequently misses lesions in the rectosigmoid, which are within reach of the examining finger and proctoscope. Several representative case summaries are included.

PHILIP LEVITSKY.

SURGERY

FOISIE, P. S. Closure of colostomies. *New Eng. J. Med.*, 234: 464 (Apr.) 1946. The closure of colostomies in 26 cases following battle injuries is reviewed. Most of these were closed without resection and without completely freeing the bowel. In cases in which the local closure resulted in a lumen of questionable adequacy, an auxiliary stoma was made in adjacent loops. Thus, satisfactory bowel continuity was re-established with a minimal sacrifice of blood supply and with a mild postoperative course. In this series a fair amount of intraperitoneal walling-off has been encountered. The re-establishment of adequate bowel continuity and closure without disruption of this protective mechanism seemed to minimize the severity of the post-operative course and to offer some protection against leakage and soiling.

IRVING GRAY.

RUSSELL, T. H. Intestinal obstruction.

Surg. Clinics N. Am., 382 (Apr.) 1946. Colonic irrigations in the early diagnosis of bowel obstruction are of considerable diagnostic and therapeutic value, providing they are performed and interpreted properly.

Digital examination of the rectum gives valuable information in differentiating between paralytic and mechanical obstruction. In mechanical obstruction the bowel is collapsed after irrigation, while in paralytic ileus the rectal ampulla is dilated.

In pre-operative treatment of large bowel obstruction, intubation of the small intestine is useless. Appendicostomy is considered a most satisfactory way of relieving obstruction if more conservative measures fail. A one-stage resection and anastomosis is performed several days later. In small bowel obstruction, decompression is accomplished either with a Levin tube or a Miller-Abbott tube. Patients with late small bowel post-operative obstruction should be operated upon as soon as dehydration and distention have been overcome. If gangrene has occurred, primary anastomosis after resection should not be done.

In early post-operative obstruction, if the Miller-Abbott tube fails, a simple enterostomy affords relief. The first piece of dilated bowel that presents itself is selected for the site of enterostomy and no attempt to explore the peritoneal cavity should be made. Spinal anesthesia is the anesthetic of choice in operations in intestinal obstruction, either of the large or the small intestine.

FRANK G. VAL DEZ.

CAVE, H., AND ALSOP, W. E. Diverticulitis of the colon. *Surg. Clinics N. Am.*, 390 (Apr.) 1946.

An analysis of 39 out of 131 cases of diverticulitis treated surgically is given, with a mortality of 15.3%. For the most part management of diverticulitis is medical rather than surgical. With failure of the inflammatory process to subside, surgical procedures must be initiated. Fifty-six operations were performed on the 39 patients. These consisted of resection of the diseased segment with end-to-end suture in 5, and with end-to-side suture in 1; exteriorization of the diseased sigmoid loop in 2; partial defunctionalizing of the left colon by cecostomy in 7; colostomy in 7; the Devine defunctionalization of the colon in 6; side-tracking by division of the transverse colon and performance of an end-to-side or side-to-side anastomosis between the

proximal end with the lower sigmoid segment. The distal transverse colon segment is brought out as a mucous fistula and a cecostomy is performed. This was performed in 2 cases (colo-colostomy).

Abscess with local peritonitis is best handled by incision and drainage alone. The risk of waiting too long before undertaking this procedure is the possibility of perforation into the bladder, producing an entero-vesicular fistula. After drainage of the abscess has been instituted, a simple colostomy is frequently helpful.

In perforation of a diverticulum attended with generalized peritonitis, simple drainage at the site of perforation with a rubber tube may allow spontaneous closure of the perforation. Primary closure of the perforations were carried out in 4 cases. Obstruction during acute diverticulitis is best managed with a cecostomy early in the course. If of a chronic nature, a divided colostomy in the transverse colon (Devine) is preferable. Fistulous openings can be cured by surgical means.

FRANK G. VAL DEZ.

ALESON, L. A. A safety factor in gastric resection—preliminary report. *Surgery*, 19: 220 (Feb.) 1946.

The author comments upon the fact that disruption of the duodenal stump following gastric resection and anastomosis is not an unusual complication. He briefly reviews the causes of disruption. In order to prevent the development of this complication, he has perfected a T-tube which is to be placed in the anastomosis at the time of the resection. The vertical limb of the T fits into the gastric stoma and the cross bar fits into the jejunum. The tube is fenestrated in such a way as to encourage free flow of the duodenal and gastric secretions into the distal jejunum and so prevent blocking of the stoma. The tube is described as being made of material similar to that which is used for the enteric coating of capsules. It is timed to disintegrate in approximately 96 hours after introduction and may be sterilized. It is stated that the use of this tube will greatly decrease the incidence of disruption of the duodenal stump following gastric resection.

HENRY TUMEN.

PHYSIOLOGY: SECRETION

McCARTHY, H. H. The effect of vagotomy and partial gastrectomy on gastric acidity; effect of stimulation of the psychic phase in presence of tenth-normal hydrochloric acid in the stomach. *Proc. Staff Meet. Mayo Clinic*, 21: 142 (Apr.) 1946.

Dogs were trained to retain stomach tubes, and samples of gastric juice were removed by means of tap-water faucet suction. Under anesthesia, bilateral thoracic vagotomy was performed, a 3 cm. segment being resected from each vagus. Two weeks later partial gastrectomy was performed, the pyloric segment being resected and a Polya type of anastomosis completed. Marked reduction in gastric acidity resulted from the operative procedures; in fact complete anacidity was found to be the case in many of these experiments.

The introduction of N/10 HCl into the stomach inhibits the intragastric chemical phase of gastric secretion. Experiments were performed to determine the effects of HCl in the stomach on the psychic phase of gastric secretion. Liver was used for stimulation of psychic secretion and 300 cc. of N/10 HCl with phenol red as indicator was introduced into the stomach at half hour intervals for 2 hours. A high rate of secretion was found in most instances, though the rate of secretion dropped towards the end of the two hour period. The roles of the three phases of gastric secretion, relative to the occurrence of hyperacidity and peptic ulcer, are brought up and it is shown how the various phases can be studied and evaluated individually.

FRANK NEUWELT.

METABOLISM AND NUTRITION

CULLINAN, E. R., KEKWICK, A., WATTS, A. S., AND TITMAN, W. L. Description of an outbreak of beriberi with special reference to the aetiology of beriberi and epidemic dropsy. *Quart. J. Med.*, 15: 91 (Apr.) 1946.

The authors describe an outbreak of a syndrome clinically indistinguishable either from beriberi or epidemic dropsy in a group of African troops in an isolated garrison. The epidemic was apparently produced by a

lack of thiamin, which was destroyed during the cooking of old contaminated rice. The authors postulate that possibly epidemic dropsy and beriberi are the same disease, caused by the destruction of thiamin in cooking the food rather than by its primary absence.

FRANK G. VAL DEZ.

COOKE, W. T., ELKES, J. J., FRAZER, A. C., PARKES, J., PEENEY, A. L. P., SAMMONS, H. G., AND THOMAS, G. Anomalies of intestinal absorption of fat. I. The determination and significance of faecal fat. *Quart. J. Med.*, 15: 141 (Apr.) 1946.

The correlation of dietary and fecal fat as fatty acid is suggested as being sufficient for the detection of a defect in fat absorption. Fat balance tests on a 50 g. fat intake were carried out on 120 patients; 41 controls showed an absorption of more than 95% of fat (variations between 91 and 99%), and 29 cases of idiopathic steatorrhea showed an average absorption of 73% (range 29-91%). Several other types of steatorrhea were also studied.

Microscopic examination of feces for detecting abnormal fat absorption, and estimation of the percentage of fat in dried feces, were not found to be useful or reliable criteria in the differentiation between normal and abnormal absorption.

Percentage hydrolysis of fecal fat was found to be of little value in the diagnosis of pancreatic disease.

FRANK G. VAL DEZ.

ALEXANDER, B., LANDWEHR, G., AND MITCHELL, F. Studies of thiamine metabolism in man. II. Thiamine and pyrimidine excretion with special reference to the relationship between injected and excreted thiamine in normal and abnormal subjects. *J. Clin. Invest.*, 25: 294 (May) 1946.

A well regulated experiment on 10 subjects was carried out over a total period of several months. Six of these were normal persons, 1 had hyperthyroidism, and 3 were chronic diabetics. One diabetic also had carcinoma of the pancreas. Increasing doses of thiamine were given intramuscularly, varying from 0.5 mg. to 100 mg., and in one case up

to 144 mg., daily. The daily oral intake of each subject, in addition to that given parenterally, was calculated from standard tables.

It was found that the excretion of thiamine into the urine by normal subjects is directly related to the amount of the vitamin administered. The 3 subjects with diabetes and the one with hyperthyroidism deviated significantly from the normal pattern of thiamine excretion. The sequence of events following the parenteral administration of thiamine may be regarded as follows: the injected vitamin enters the blood stream and is rapidly transported to the tissues where it is converted, at least in part, to cocarboxylase. Some of the thiamine is converted to pyrimidine. This, together with whatever thiamine cannot be retained in the tissues, is retransported to the kidneys and is excreted in the urine. Thiamine overflow into the urine continues at a certain rate for many days after injection of the thiamine is discontinued.

Since the major portion of thiamine administered in daily doses of more than 10 mg. is rapidly excreted in the urine, and since doses of more than 34 mg. do not result in greater storage of thiamine in the tissues, there seems no justification for the use of larger doses parenterally.

SAM OVERSTREET.

ALEXANDER, B., AND LANDWEHR, G. Studies of thiamine metabolism in man. I. Thiamine balance. The normal requirement of vitamin B₁ and the role of fecal thiamine in human nutrition. *J. Clin. Invest.*, 25: 287 (May) 1946.

A very complete experiment was carried out on one subject on a freely selected diet of approximately 2400 Calories daily. During one week a complete analysis was made of the equivalent in food consumed and of the excreted urine and feces. In another 51-day period the subject, in addition to his food, received intramuscular doses of thiamine daily varying from .05 to 145 mg. The claim that thiamine is absorbed from the large bowel was tested by the administration of a retention enema containing twice the amount of thiamine and cocarboxylase found in the average daily stool and retained for 24 hours.

Conclusions reached were as follows: (1) The minimal requirement in a normal male, whose caloric intake was 2400 Calories daily, was found to be .44 mg. per 1000 Calories. This figure corresponds fairly well with that established by the Committee on Food and Nutrition of the National Research Council, that 1.8 mg. is the optimal daily intake of thiamine for a moderately active man whose caloric intake is 3000 Calories. (2) Thiamine and cocarboxylase, when administered in physiological amounts by retention enema, were not absorbed from the large bowel.

SAM OVERSTREET.

PHARMACOLOGY

BOYD, E. M., CLARK, K. L., AND ELLIOTT, R. C. The choleretic action of the allyl ester of cinchophen (atoquinol). *J. Lab. Clin. Med.*, 30: 943 (Nov.) 1945.

Cinchophen and its allyl ester, commonly known as atoquinol, have choleretic action in the dog. Fifteen dogs with chronic biliary fistulae were given the drugs in doses of 0.1 g./kg. body weight, mixed with the food. Both drugs gave similar qualitative and quantitative results. The 24-hour volume output of bile, the specific gravity, and the total solids were increased during the first two days. There was an increase in the potassium and inorganic phosphate content. No significant changes were noted in the contents of sodium, chloride, total fatty acids, total cholesterol, ester cholesterol, free cholesterol, bilirubin, and bile acids. The relative viscosity of the bile was significantly decreased.

PHILIP LEVITSKY.

ANATOMY

KELLSALL, M. A. Anomalies in the small intestine and cecum of inbred strains of mice. *Anat. Rec.*, 95: 1 (May) 1946. Statistical data on visceral anomalies are scant because of the difficulty of making such observations on the internal organs of a large number of animals. The guts of 1,299 mice of 8 inbred strains were examined. Meckel's diverticulum was the only gross anomaly observed in the small intestine; it was present in 10 instances (0.77%). In man, the incidence of Meckel's diverticulum

is reported to be between 2 and 3%. Five diverticula were present in male mice and a like number in female mice. Relationships of the diverticulum to the Peyer's patches were not consistent within strains or between strains. One anomalous cecum was found in the entire series; the orifices of the ileum and colon entered at widely separated points instead of the normal proximal positions.

FRANK NEUWELT.

DURAN-JORDA, F. A micro-incineration study of the flat epithelial layer covering the alimentary tract. *Brit. J. Surg.*, 33: 346 (Apr.) 1946.

Since staining is uncertain for the demonstration of both intra-cellular mucus and the supposed mucus covering the mucous membrane, micro-incineration technique is advocated and the procedure is described in some detail. By such a method the organic nature of the flat epithelial layer covering the gastric, intestinal, and gall-bladder mucosae, as previously described by the author, is demonstrated with more certainty. The description of this layer will be quite interesting to those previously unaware of its existence.

J. DUFFY HANCOCK.

MISCELLANEOUS

HESSELBROCK, W. B., LIPPINCOTT, S. W., AND PALMER, E. D. Large-scale routine examinations of stool for parasites. *Am. J. Clin. Path.*, 16: 264 (Apr.) 1946.

A total of 14,250 stools from 2,464 patients were examined at the Harmon General

Hospital, Longview, Texas, in order to obtain data regarding intestinal parasitic infestation in patients received from the Pacific Area, the European and Mediterranean Theatres, and the Zone of the interior only, and also to evaluate the efficiency of the different technics used. The direct smear, the zinc sulfate flotation method, sedimentation by gravity, and sedimentation by centrifugal technics were the methods compared.

In resumé, 17.4% of 1,261 men from the Pacific Area, excluding those with Schistosomiasis, showed parasitic infections in the stools; 8.4% of such infections were found in 535 men from the European and Mediterranean Theatres, and 9.7% among 176 men from the zone of the Interior only. Of these infections, hookworm was the most frequent: 10.8%, 5.0% and 6.8% respectively. Endamoeba histolytica occurred in 1.0%, 0.4% and 1.1% respectively. Giardia lamblia was found in but few cases because of the general prophylactic and therapeutic use of atabrine. Of the methods used, the zinc sulfate centrifugal flotation method proved to be the most efficient. It gave positive results more than twice as often as the other methods, but it entailed more than 30 times the effort. For routine work the direct smear and a modified zinc sulfate sedimentation method were used. Although the hookworm infection was the most frequent it was light in character and no clinical hookworm disease was noted in the patients.

N. W. JONES.

INDEX

OR

MANUSCRIPTS PUBLISHED

ARRANGED BY AUTHOR AND SUBJECT

(Ed.) Signifies Editorial

(Com.) Signifies Comment

- Aaron, A. H. The president's address, 153
Allergy, food, cause of puzzling "nervous storms"
(Case Report), 241
Allergy, food, use of elimination diets and food
diaries in the diagnosis of (Ed.), 249
Alteracoes Hepaticas Na Tireotoxicose (Book
Review), 139
Althausen, T. L., Eiler, J. J., and Stockholm, M.
B vitamins, intestinal absorption and food
utilization. I. Studies in rats on diets defi-
cient in certain B vitamins and during
recovery from such diets, 469
Althausen, T. L., Eiler, J. J., and Stockholm, M.
B vitamins, intestinal absorption and food
utilization. II. Metabolism studies in rats
on diets deficient in certain B vitamins and
during recovery from such diets, 555
Alvarez, W. C., Puzzling "nervous storms" due
to food allergy (Case Report), 241
Amebic disease of cecum: clinical and radiolog-
ical aspects, 535
American Board of Internal Medicine, report of
advisory committee on gastroenterology
of, 261
Amino acid alimentation in gastro-intestinal
diseases, 442
Anorexia nervosa. A mental disease (Ed.), 693
Anoxia test as an aid in diagnosis of coronary
insufficiency (Com.) 376
Appendicitis, acute, recent decline in mortality
from (Com.) 494
Arteriosclerosis, gastric, hematemesis associated
with (Clin. Path. Conf.), 231
Atkinson, A. J. Clinical pathological confer-
ence, 121, 243, 477
—. See Greengard, et al., 625
Autonomic nervous system (Book Review), 583
Avey, H. T. See Musick, et al., 332

Backache due to intra-abdominal disease, 294
Bachrach, W. H. See Pollard, et al., 136
—. See Pollard, et al. (Com.), 254

Bacteriological and parasitic studies of intes-
tinal contents of patients with sprue, 306
Bargen, J. A. See Remington, et al., 442
Benadryl, effect on histamine-induced gastric
acidity in man, 100
—, gastric secretory response of patients having
duodenal ulcer, 91
Berg, B. N. Vascular changes in the mucosa in
experimental nutritional gastritis, 340
Biliary tract, cholecystitis and cholelithiasis in
identical twins (Case Report), 685
—, treatment of post-operative biliary dys-
kinesia, 414
Biochemistry, medical (Book Review), 698
Bleeding, gastrointestinal, in hereditary hemor-
rhagic telangiectasia, 199
Block, M. See Pollard, et al. 136
—. See Pollard, et al. (Com.), 254
Books, war victims (Com.), 259
Brown, P. W. Bacillary dysentery, 525
Brunschwig, A. See Morton and Brunschwig,
314

Caffeine and "peptic" ulcer (Com.), 576
— test meal response-gastric secretion in duo-
enal ulcer in remission, 332
Camp, J. D. See Wilbur and Camp, 535
Cancer, new treatment of (Com.), 494
Carbonic anhydrase theory of gastric acid secre-
tion: in memoriam (Com.), 374
— anhydrase theory of HCl formation (Com.),
375
Carcinoma, stomach, relation of gastroscopy to
roentgenology in diagnosis, 285
Cecum, amebic disease of: clinical and radiolog-
ical aspects, 535
Chamberlin, D. T. Military gastroenterology
—summing up, 162
Chemistry of food and nutrition (Book Reviews),
698
Chen, K. K. See Wakim, et al., 213
Cholecystitis, etiology of, 665
— and cholelithiasis in identical twins, 685

- Cholecystokinin and secretin, separation and assay of, 108
- Cholesterol apparently protects against the development of certain arterial lesions (Ed.), 575
- Clinical pathological conference, 118, 121, 126, 477, 562, 687
- Colitis, chronic non-specific ulcerative, complications of, 55
- , ulcerative, etiology of. Analytical review of the literature, 67
- , ulcerative, unusual initial onset of, with exsanguinating bowel hemorrhage (Case Report), 483
- , ulcerative, chronic, succinyl sulfathiazole (sulfasuxidine) in treatment, 549
- Collins, E. N., and Hewlett, J. S. Succinyl sulfathiazole (sulfasuxidine) in the treatment of chronic ulcerative colitis, 549
- Colon, color changes in the mucosa of, as affected by food and psychic stimuli (Ed.), 574
- Colp, R. Treatment of post-operative biliary dyskinesia, 414
- Cornell conferences on therapy, vol. I. (Book Review), 379
- Coronary insufficiency, anoxia as an aid in diagnosis of (Com.), 376
- Crohn, B. B., Rouse, M. O., and Smith, H. W. Relationship of trauma to perforation of peptic ulcer, 456
- Cummins, G. M., Jr., Grossman, M. I., and Ivy, A. C. Study of the time of "healing" of peptic ulcer in a series of sixty-nine cases of duodenal and gastric craters, 20
- Curbelo, A. See Milanes, et al., 306
- Cytochemistry, recent advances in (Com.), 256
- Davenport, H. W. Carbonic anhydrase theory of gastric acid secretion: in memoriam (Com.), 374
- Diagnosis, medical (Book Review), 264
- Diabetes mellitus, the modern treatment of (Book Review), 496
- Diarrhea, chronic, in military personnel returning from the tropics, 528
- , recurrent, due to infection with *Salmonella typhimurium*, 522
- Differential diagnosis of 207 hospitalized cases of peptic ulcer, 168
- Doublet, H. Separation and assay of secretin and cholecystokinin, 108
- Dysentery, bacillary, 525
- , in American troops in the Middle East, 533
- Dyskinesia, biliary, treatment of post-operative, 414
- Dyspepsia, chronic non-ulcerative, correlated gastroscopic and psychiatric studies of soldiers with, 177
- Eiler, J. J. See Althausen, et al., 469
- . See Althausen, et al., 555
- Elman, R. Surgery in acute pancreatitis, 656
- Enema, markedly hypertonic, acute enterocolitis and death resulting from (Case Report), 364
- Enterocolitis, acute, and death resulting from markedly hypertonic enema (Case Report), 364
- Enterogastrone, effectiveness of in the prophylaxis of recurrences of experimental and clinical peptic ulcer, 625
- Esophagus, peptic ulcer of, 314
- Estudo Medio-Cirurgico da Esquistosomiasis de Manson (Book Review), 584
- Fibrositis and myositis of psoas muscle, abdominal pain due to (Ed.), 489
- Fistula, gastrocolic: clinical and experimental study, 511
- Frank, W. Hematemesis associated with gastric arteriosclerosis (Case Report), 231
- Friedman, M. H. F. See Sandweiss, et al., 38
- Gallbladder, cholecystitis and cholelithiasis in identical twins (Case Report), 685
- , etiology of cholecystitis, 665
- , treatment of post-operative biliary dyskinesia, 414
- Gastric acid secretion, the carbonic anhydrase theory of, (Com.), 374
- Gastritis, experimental nutritional, vascular changes in mucosa, 340
- Gastric secretion in duodenal ulcer in remission; response to caffeine test meal, 332
- Gastroscopy and psychiatry, correlated studies of soldiers with chronic non-ulcerative dyspepsia, 177
- , relation to roentgenology in diagnosis of carcinoma of stomach, 285
- Gastroenterology, vol. III. (Book Review), 264
- Gastrointestinal bleeding in hereditary hemorrhagic telangiectasia, 199
- Ginsberg, R. S. and Ivy, A. C. Etiology of ulcerative colitis: analytical review of the literature, 67

- Greengard, H., Atkinson, A. J., Grossman, M. I., and Ivy, A. C. The effectiveness of parenterally administered "enterogastrone" in the prophylaxis of recurrences of experimental and clinical peptic ulcer, 625
- Grimson, K. S. See Ruffin, et al., 599
- Grossman, M. I. See Cummins, et al., 20
- . See Greengard, et al., 625
- Halsted, J. A., Schwartz, I. R., Rosen, S. R., Weinberg, H., and Wyman, S. M. Correlated gastroscopic and psychiatric studies of soldiers with chronic non-ulcerative dyspepsia, 177
- Heid, J. B. See Thompson, et al., 320
- Hellbaum, A. A. See Musick, et al., 332
- Hematemesis associated with gastric arteriosclerosis (Case Report), 231
- , a study of underlying causes, 320
- Hemorrhage, exsanguinating bowel, unusual & initial onset of ulcerative colitis with, 483
- in peptic ulcer, history of, 450
- Hepatic tests, results of, in chronic hepatitis without jaundice, 1
- Hepatitis, infectious, laboratory aids in diagnosis and management of, 393
- Hewlett, J. S. See Collins and Hewlett, 549
- Hirsutism in women (Ed.), 490
- Histamine and gastric secretion in relation to anti-histamine drugs (Com.), 134
- induced gastric acidity in man, effect of benadryl on, 100
- Hollander, F. Carbonic anhydrase theory of HCl formation (Com.), 375
- The insulin test for the presence of intact nerve fibers after vagal operations for peptic ulcer, 607
- Hopps, H. C. See Musick, et al., 332
- Hormones, gastrointestinal, separation and assay of secretin and cholecystokinin, 108
- Horton, B. T. See McElin and Horton, 100
- Hydrochloric acid formation, carbonic anhydrase theory of (Com.), 375
- Hypertony, studies in and the prevention of disease (Book Review), 496
- Insulin, test for presence of intact nerve fibers after vagal operations for peptic ulcer, 607
- Intestine, activity of, effects of B-dimethylaminoethyl benzilate hydrochloride on, 213
- , amebic disease of the cecum: clinical and radiological aspects, 535
- , effects of B vitamins on intestinal absorption and food utilization, 555
- , parasites of, in service personnel in the South Pacific with special reference to the incidence and treatment of strongyloidiasis, 650
- , recent decline in mortality from acute appendicitis, 494
- , small, absorption and food utilization in rats on diets deficient in certain B vitamins, 555
- , —, and stomach, effect of glucose on the motility of, 218
- , large, bacillary dysentery, 525
- , —, chronic diarrhea in military personnel returning from the tropics, 528
- , —, color changes in the mucosa of the colon as affected by food and psychic stimuli (Ed.), 574
- , —, complications of chronic non-specific ulcerative colitis, 55
- , —, dysentery in American Troops in the Middle East, 533
- , —, enterocolitis, acute, and death resulting from enema (Case Report), 364
- , —, etiology of ulcerative colitis, 67
- , —, recurrent diarrhea due to infection with *Salmonella typhimurium*, 522
- , —, succinyl sulfathiazole (sulfasuxidine) in treatment of chronic ulcerative colitis, 549
- , —, unusual initial onset of ulcerative colitis with exsanguinating bowel hemorrhage (Case Report), 483
- Ivy, A. C. See Cummins, et al., 20
- . See Greengard, et al., 625
- . See Ginsburg and Ivy, 67
- . See Roth and Ivy, 576
- Ivy, J. S. Effect of pilocarpine on mucus secretion by the pyloric mucosa, 224
- Jobb, E. Unusual initial onset of ulcerative colitis with exsanguinating bowel hemorrhage (Case Report), 483
- Jones, C. R. Obituary, 267
- Jordan, S. Frank Howard Lahey, the Friedenwald Medalist for 1946 (Ed.), 131
- Kenamore, B. Chronic diarrhea in military personnel returning from the tropics, 528
- Kirk, R. C. Differential diagnosis of 207 hospitalized cases of peptic ulcer, 168
- Kirklin, B. R. See Moersch and Kirklin, 285
- Kiskadden, R. M. See Renshaw, et al., 511
- Klemperer, P. recent advances in cytochemistry (Com.), 256

- Kouri, P. See Milanes, et al., 306
- Kraemer, M. Clinical findings in American soldiers released from a German prison camp, 191
- Clinical pathological conference, 687
- Kushlan, S. D. Gastrointestinal bleeding in hereditary hemorrhagic telangiectasia. Historical review and case report with gastroscopic findings and Rutin therapy, 199
- Lahey, Frank Howard. The Friedenwald Medalist for 1946 (Ed.), 131
- (Ed.), 133
- Lindsay, S. Acute enterocolitis and death resulting from markedly hypertonic enema (Case Report), 364
- Lipp, W. F. Acute pancreatitis. Report of a case showing serum calcium changes as well as Grey Turner sign. (Case Report), 569
- Liver, Alteracoes Hepaticas Na Tireotoxicose (Book Review), 139
- . Laboratory aids in diagnosis and management of infectious hepatitis, 393
- . Nutritional deficiency as a probable cause of hepatic damage in repatriated prisoners of war, 430
- , results of hepatic tests in chronic hepatitis without jaundice, 1
- Lundy, J. S. See Remington, et al., 442
- Lung tumor with prominent abdominal changes (case report), 355
- Lymphogranuloma venereum, the virus of, (Com.), 696
- Margolis, G. See Ruffin and Margolis (Clinical Pathological Conference), 118
- McElin, W., and Horton, B. T. Clinical observations on the use of benadryl: its effect on histamine-induced gastric acidity in man, 100
- Medical education and practice in Germany during World War II (Com.), 493
- Meienberg, L. J., and Snell, A. M. Nutritional deficiency as a probable cause of hepatic damage in repatriated prisoners of war, 430
- Men without guns (Book Review), 698
- Metabolism studies in rats on diets deficient in certain B vitamins, 555
- Milanes, F., Curbelo, A., Rodriguez, A., Kouri, P., and Spies, T. D. Note on bacteriological and parasitic studies of the intestinal contents of patients with sprue, 306
- Moersch, R. U., Rivers, A. B., and Morlock, C. G. Some results of the gastric secretory response of patients having duodenal ulcer noted during the administration of benadryl, 91
- Moersch, H. S., and Kirklin, B. R. Gastroscopy and its relationship to roentgenology in the diagnosis of carcinoma of the stomach, 285
- Moore, A. B. Obituary, 268
- Morgan, F. M. See Thompson, et al., 320
- Morlock, C. G. See Moersch, et al., 91
- Morton, D. R., and Brunschwig, A. Peptic ulcer of the esophagus; report of a patient with a 10 year follow-up, 314
- Motility of the stomach and small intestine, effect of glucose on, 218
- Musick, V. H., Avey, H. T., Hopps, H. C., and Hellbaum, A. A. Gastric secretion in duodenal ulcer in remission—response to the caffeine test meal, 332
- Mustard gas as a substitute for roentgenotherapy (Com.), 495
- Myositis and fibrositis of psoas muscle, abdominal pain due to (Ed.), 489
- Nausea, cause of (Ed.), 371
- Neefe, J. R., and Reingold, J. G. Laboratory aids in the diagnosis and management of infectious hepatitis, 393
- . Results of hepatic tests in chronic hepatitis without jaundice, 1
- Northup, D. W. See Van Liere, et al., 218
- Nutrition and food, chemistry of, 698
- Obesity, the management of (Book Review), 584
- Obituaries, Jones, C. R., 267
- , Moore, A. B., 268
- Opium and its derivatives, a drug which doubles the analgesic effects of (Com.), 697
- Oyster, J. M. See Thompson, et al., 320
- Palmer, W. L. See Ricketts and Palmer, 55
- Pancreatitis, acute, report of a case showing serum calcium changes as well as Grey Turner sign (Case Report), 569
- acute, surgery in, 656
- Parasitic and bacteriological studies of intestinal contents of patients with sprue, 306
- Penicillin, the approaching synthesis of, (Ed.), 371
- Penner, A. Recurrent diarrhea due to infection with *Salmonella typhimurium*, 522

- Person in the body (Book Review), 265
 Pilocarpine, effect of on mucus secretion by the pyloric mucosa, 224
 Podolsky, H. M. See Sandweiss, et al., 38
 Pollard, H. M. Clinical pathological conference, 126, 562
 —, Bachrach, W. H., and Block, M. Observations on the healing of gastric ulcers (Com.), 136
 —, —. Supradiaphragmatic vagotomy for ulcer (Com.), 254
 Powell, C. E. See Wakim, et al., 213
 President's address, 153
 Presidential address (Ed.), 249
 Preventive medicine and public health (Book Review), 698
 Proctology, ambulatory (Book Review), 139
 Pruitt, R. D. Anoxia test as an aid in diagnosis of coronary insufficiency (Com.), 376
 Psoas muscle, abdominal pain due to fibrosis and myositis (Ed.), 489
 Psychiatric and gastroscopic studies, correlated, in soldiers with chronic non-ulcerative dyspepsia, 177
 Psychosomatic medicine. The person in the body (Book Review), 265
 Pyloric mucosa, effect of pilocarpine on mucus secretion by, 224
 Radiology. Amoebic disease of cecum, 535
 —. Mustard gas as substitute for roentgenotherapy (Com.), 495
 —. Relation to gastroscopy in diagnosis of carcinoma of stomach, 285
 —. Roentgen diagnosis of diseases of the gastro-intestinal tract (Book Review), 496
 Rehfuss, M. E. Etiology of cholecystitis, 665
 Reingold, J. G. See Neefe and Reingold, 393
 Remington, J. H., Bargen, J. A., and Lundy, J. S. Amino acid alimentation in gastrointestinal diseases, 442
 Renshaw, R. J. F., Kiskadden, R. M., and Templeton, F. E. Gastrocolic Fistula: a clinical and experimental study, 511
 Ricketts, W. E., and Palmer, W. L. Complications of chronic non-specific ulcerative colitis, 55
 Rivers, A. B. See Moersch, et al., 91
 Rodriguez, A. See Milanes, et al., 306
 Rosen, S. R. See Halsted, et al., 177
 Roth, J. A., and Ivy, A. C. Caffeine and "peptic ulcer." (Com.), 576
 Rouse, M. O. See Crohn, et al., 456
 Ruffin, J. M., and Margolis, G. Clinical pathological conference, 118
 —, Grimson, K. S., and Smith, R. C. Effect of transthoracic vagotomy upon the clinical course of patients with peptic ulcer, 599
 —. Vagotomy in treatment of ulcer (Ed.), 692
 Rutin therapy and gastroscopic findings in hereditary hemorrhagic telangiectasia, 199
 Sandweiss, D. J., Friedman, M. H. F., Sugarman, M. H., and Podolsky, H. M. Nocturnal gastric secretion—Part II. Studies on normal subjects and patients with duodenal ulcer, 38
 Schiff, L. A case of lung tumor with prominent abdominal changes (Case Report), 355
 Schwartz, I. R. See Halsted, et al., 177
 Secretin and cholecystokinin, separation and assay of, 108
 Shaffer, K. R. Books-war victims (Com.), 259
 Smith, H. W. See Crohn, et al., 456
 Smith, R. C. See Ruffin, et al., 599
 Snell, A. M. See Meienberg and Snell, 430
 Spies, T. D. See Milanes, et al., 306
 Sprue. Bacteriological and parasitic studies of the intestinal contents, 306
 Stenosis, hypertrophic pyloric, in the adult, 464
 Stickney, J. C. See Van Liere, et al., 218
 Stockholm, M. See Althausen, et al., 469, 555
 Stomach and small intestine, effect of glucose on the motility of, 218
 —, carbonic anhydrase theory of gastric acid secretion (Com.), 374
 —, carbonic anhydrase theory of HCl formation (Com.), 375
 —, carcinoma of, relation of roentgenology to gastroscopy in diagnosis, 285
 —, effect of benadryl on histamine-induced gastric acidity in man, 100
 —, effect of pilocarpine on mucus secretion by pyloric mucosa, 224
 —, effect of transthoracic vagotomy upon the clinical course of patients with peptic ulcer, 599
 —, gastric secretion in duodenal ulcer in remission, response to the caffeine test meal, 332
 —, gastric secretory response of patients having duodenal ulcer, noted during administration of benadryl, 91
 —, gastric tumors produced in insects by cutting nerve to the stomach (Ed.), 252
 —, gastrocolic fistula, clinical and experimental study, 511

- Stomach and small intestine, gastrointestinal bleeding in hereditary hemorrhagic telangiectasia, 199
- , hematemesis associated with gastric arteriosclerosis (Case Report), 231
- , hematemesis of: study of underlying causes, 320
- , histamine and gastric secretion in relation to anti-histamine drugs (Com.), 134
- , history of hemorrhage in peptic ulcer, 450
- , hypertrophic pyloric stenosis in the adult, 464
- , insulin test for presence of intact nerve fibers after vagal operations for peptic ulcer, 607
- , nocturnal secretion, studies on normal subjects and patients with duodenal ulcer, 38
- , observations on the healing of gastric ulcers (Com.), 136
- , relationship of trauma to perforation of peptic ulcer, 456
- , study of the time of "healing" of peptic ulcer in a series of sixty-nine cases of duodenal and gastric craters, 20
- , supradiaphragmatic vagotomy for ulcer (Com.), 254
- , Tratamiento Dietetico De Los Gastrectomizados (Book Review), 380
- , vascular changes in mucosa in experimental nutritional gastritis, 340
- , studies of peptic ulcer (Ed.), 372
- Strongyloidiasis, intestinal parasites in service personnel in the South Pacific, 650
- Sugarman, M. H. See Sandweiss, et al., 38
- Sulfonamides, succinyl sulfathiazole (sulfasuxidine) in the treatment of chronic ulcerative colitis, 549
- Surface active agents (Book Review), 380
- Surgery in acute pancreatitis, 656
- Telangiectasia, hereditary hemorrhagic, with gastrointestinal bleeding, 199
- Templeton, F. E. See Renshaw, et al., 511
- Tesler, J. Cholecystitis and cholelithiasis in identical twins (Case Report), 685
- Thompson, H. L., Oyster, J. M., Heid, J. B., and Morgan, F. M. Hematemesis: study of underlying causes, 320
- Tracey, M. L. See Wilkinson and Tracey, 450
- Trauma, relationship to perforation of peptic ulcer, 456
- Tratamiento Dietetico De Los Gastrectomizados (Book Review), 380
- Tumors, gastric, produced in insects by cutting the nerve to the stomach (Ed.), 252
- Tumen, H. J., and Yaskin, J. C. Backache due to Intra-abdominal disease, 294
- Ulcer, supradiaphragmatic vagotomy for (Com.), 254
- , vagotomy in treatment of (Ed.), 692
- , duodenal, gastric secretory response during administration of benadryl, 91
- , —, in remission, gastric secretion of, in response to the caffeine test meal, 332
- , —, nocturnal secretion in subjects and patients with—Part II., 38
- , gastric, observations on healing time (Com.), 136
- , peptic and caffeine (Com.), 576
- , —, differential diagnosis of 207 hospitalized cases of, 168
- , —, effectiveness of parenterally administered "enterogastrone" in the prophylaxis recurrences of, 625
- , —, effect of transthoracic vagotomy upon the clinical course of patients with, 599
- , —, history of hemorrhage in, 450
- , —, insulin test for the presence of intact nerve fibers after vagal operations for, 607
- , —, of the esophagus, 314
- , —, perforation, relationship to trauma, 456
- , —, studies among soldiers in the Mediterranean Theatre of Operations (Ed.), 372
- , —, study of the time of "healing" in a series of sixty-nine cases of duodenal and gastric craters, 20
- , —, surgery, gastrocolic fistula, 511
- Vagotomy, insulin test for presence of intact nerve fibers after vagal operations for peptic ulcer, 607
- , in treatment of ulcer (Ed.), 692
- , supradiaphragmatic, for ulcer (Con.), 254
- , transthoracic, effect of upon clinical course of patients with peptic ulcer, 599
- Van Liere, E. J., Northup, D. W., and Stickney, J. C. Effect of glucose on the motility of the stomach and small intestine, 218
- Vitamins B, effect on intestinal absorption and food utilization, 469, 535
- Vitamins in Medicine (Book Review), 382
- Vorhaus, M. G. Hypertrophic pyloric stenosis in the adult, 464

- Wakin, K. G., Powell, C. E., and Chen, K. K.
Effects of B-dimethylaminooethyl benzilate hydrochloride on intestinal activity, 213
- War Medicine, books—war victims (Com.), 259
- , chronic diarrhea in military personnel returning from the tropics, 528
- , clinical findings in American soldiers released from German prison camp, 191
- , correlated gastroscopic and psychiatric studies of soldiers with chronic non-ulcerative dyspepsia, 177
- , dysentery in American troops in the Middle East, 533
- , intestinal parasites in service personnel in South Pacific with special reference to incidence and treatment of strongyloidiasis, 650
- , medical education and practice in Germany during World War II. (Com.), 493
- , military gastroenterology, summing up, 162
- , nutritional deficiency as a probable cause of hepatic damage in repatriated prisoners of war, 430
- , studies of peptic ulcer (Ed.), 372
- Weinberg, H. See Halsted, et al., 177
- Wilbur, D. L., and Camp, J. D. Amebic disease of the cecum: clinical and radiological aspects, 535
- Wilkinson, S. A., and Tracey, M. L. History of hemorrhage in peptic ulcer, 450
- Willard, J. Intestinal parasites in service personnel in the South Pacific; with special reference to the incidence and treatment of strongyloidiasis, 650
- Wirts, C. W., Jr. Dysentery in American troops in the Middle East, 533
- Wyman, S. M. See Halsted, et al., 177
- Yaskin, J. C. See Yaskin and Tumen, 294



INDEX

ABSTRACTS

- Absorption, intestinal, influence of induced changes in blood plasma osmotic activity, 149
—, iron, effects of inflammation (turpentine abscess) on, 596
- Alimentary tract, a micro-incineration study of the flat epithelial layer covering the, 712
— of the newborn, surgical emergencies of, 282
- Amebiasis, diagnosis of, 504
—, treatment of, with special reference to chronic amebic dysentery, 384
- , the clinical significance of deformity of the cecum in, 384
- Amino acids, value in surgical repair, 282
— and B complex vitamins, the role of, in muscle metabolism and balanced nutrition, 597
- Anastomosis, intestinal, preliminary report of a method for the prevention of leakage of, 595
- Anatomy, a micro-incineration study of the flat epithelial layer covering the alimentary tract, 712
- Anemia, activity of synthetic *Lactobacillus casei* factor ("folic acid") as an anti-pernicious anemia substance, 277
—, anti-pernicious factor, urinary excretion of, 277
—, chronic hemolytic, observations on the effect of fat content of the diet and multiple red cell transfusions, 706
—, observations of the anti-anemic properties of synthetic folic acid, 277
—, pernicious and familial acholuric jaundice, a note on the differential diagnosis of, 598
—, —, treatment of, 706
- Anorectal disease, genito urinary, symptoms of, 509
- Anoxia, influence of, on the gastric HCl secretion, 596
- Anus and colon, carcinoma of, 503
- Appendicitis, acute, diagnosis of, in the presence of diarrhea, 701
—, —, local use of sulfanilamide in the treatment of, 142
—, —, treatment of, 271
- , unusual types of, 587
—, left-sided, a case of, 144
—, —, in a dextro-cardiac patient, 502
- Appendix, vermiform, large intestine and urinary bladder, duplication of, 281
- Atresia, congenital, of the common bile duct, 704
- Beriberi, description of an outbreak of, with special reference to the etiology of epidemic dropsy, 710
- Bile salts, effect on the experimental production of ulcer in the dog, 279
- Biliary tract, abnormal human, excretion and concentration of penicillin and streptomycin in, 506
—, advanced carcinoma of the extrahepatic bile ducts: cholangiocholecystocholedectomy, 146
—, alterations in the properties of dog hepatic bile with increasing age of the chronic biliary fistula, 280
—, choleretic action of the allyl ester of cinchophen, 711
—, congenital atresia of the common bile duct, 704
—, —, cystic dilatation of common duct, 388
—, —, obliteration of bile ducts and icterus gravis neonatorium, 387
—, deaths from surgical diseases of, 591
—, diverticula of the colon versus gallstones, 386
—, drainage, dynamics of, 147
—, etiology of gallstones, 145
—, hydrops of gallbladder, 591
—, investigations of the phosphatase activity in serum and organs after ligation of the common bile duct in dogs, 703
—, management of post-operative choledocholithiasis, use of solution G, 145
—, obstruction in rabbits, experimental, studies on serum phosphatase activity in relation to, 592
—, pancreatitis, an anatomic study of the pancreatic and extrahepatic biliary system, 276
—, papilloma of the gallbladder, 703
—, Penicillin in acute cholecystitis, 592

- Biliary tract, reconstruction of the common duct with vitallium tubes, 146
- , studies of serum phosphatase activity in relation to experimental biliary obstruction in rabbits, 145
- , traumatic rupture of the gallbladder, choleperitoneum, 388
- Blood, chronic hemolytic anemia, observations on the effect of fat content on the diet and multiple red cell transfusions, 706
- , group substances in human gastric contents, 392
- Brucellosis and peptic ulcer, 390
- Burns, experimental, blood histamine level in, 507
- , gastro-duodenal ulcer following, 390
- Calcium and potassium content of secretions from noncancerous and cancerous stomachs, 500
- Cancer, gastric, hyperuricemia in, 700
- Carbon tetrachloride, effect of methionine supplements on hepatic injury produced by, 505
- Carcinoma, advanced intra-abdominal, radical resections of, 391
- , —, of the extra-hepatic bile ducts: cholangiolecystocholedochectomy, 146
- , complicating ulcerative colitis, 141
- , carcinoma, cylindroma type, of parotid gland, 499
- of the colon, 140
- of the colon and rectum, 503
- , multiple, of the stomach, 700
- of small intestine in mouse and rat, Paneth cells in, 148
- of the stomach and other viscera, direct irradiation of, 383
- , —, a ten year survey made in a general hospital, 699
- , —, correlation of gastroscopic, roentgenologic and pathologic findings, 499
- , —, evaluation of criteria useful in differentiation of benign and malignant lesions, 585
- , gastric, review of errors in diagnosis, 383
- , pancreas simulating, cancerous cyst of the tail of, 593
- , primary resection of malignant lesions of the large bowel, 590
- with submucosal lipomas of stomach, 500
- Cathartics, hydrogogue, fumaric acid salts as, 273
- Cecum and small intestine of inbred strains of mice, anomalies in, 711
- Cephalincholesterol flocculation, comparison with the thymol turbidity test, 274
- Cholangiolecystocholedochectomy, advanced carcinoma of the extrahepatic bile ducts, 146
- Cholecystitis, acute, penicillin in, 592
- Cholecystostomy, congenital atresia of the common bile duct, 704
- Choledocholithiasis, postoperative, the management of, use of solution G, 145
- Choleperitoneum, case reports and notes on, traumatic rupture of the gallbladder, 388
- Cholethiasis, relation of, to acute hemorrhagic pancreatitis, 389
- Cinchophen, choleric action of the allyl ester of atoquinol, 711
- Cirrhosis, see also liver
- , hepatic, due to choline deficiency, significance of fatty infiltration in the development of, 505
- , —, use of salt-poor concentrated human serum albumin solution in the treatment of, 705
- of liver, experimental dietary, thiouracil in the prevention of, 147
- , —, experimental, treatment of, 276
- , —, Laennec's, the plasma volume in, 592
- , —, response to an intensive combined therapy, 703
- Cobalt, elimination of, in pancreatic juice and bile of dog, as measured with its radioactive isotopes, 391
- Colectomy and ileostomy in chronic ulcerative colitis, 143
- Colitis, amebic, special reference to perforation, 272
- chronic, ulcerative, ileostomy and colectomy in, 143
- , ulcerative, complicated by carcinoma, 141
- , —, diagnosis and management of, 501
- , —, penicillin therapy in, 589
- , —, treatment of, with nisulfadine and nisulfazole, 502
- Colon and rectum, carcinoma of, 503
- , barium study and proctoscopy in the diagnosis of rectal conditions, 708
- , carcinoma of, 140
- , congenital or hereditary polyposis of, 142
- , diverticulitis of, 709
- , — of the vermiform appendix, 142

- , lower, spontaneous rupture of, with eversion of small intestine through anal orifice, 144
- , primary anastomosis in carcinoma of, 279
- , redundancy of, 502
- , sigmoid, peritonitis following malignant obstruction and free perforation of, 701
- Colostomy, closure of, 708
- , improved method for extraperitoneal closure of, 149
- Constipation, chronic, management of, 386
- Cyst, thoracic gastric, 586

- Decholin and Degalol, choleretic action of, in chronic biliary fistula dogs, 275
- Diarrhea, diagnosis of acute appendicitis in the presence of, 701
- Diverticulitis of the colon, 709
- Diverticulum, Meckel's with report of a case of intussusception due to its invagination, 503
 - of ileum and jejunum, 589
- Dropsey, epidemic and beriberi, etiology of, description of an outbreak of beriberi, 710
- Duodenum, congenital obstruction of, 588
- Duodenal obstruction caused by annular pancreas, 593
 - , complete, in the newborn, 589
- Dysentery, bacillary, sulfonamides in, 383
- , chronic amebic, treatment of, 384
- , surgical treatment of lesions of the bowel, 385

- Electrophoresis, the number and relative concentrations of protein constituents of canine pancreatic juice, 280
- Endocrine glands, relation to the gastric secretory depressant in urine, 150
- Enteritis, chronic, significance of, 386
- , regional, chronic nonspecific, 273
- Esophagogastronomy, transthoracic, for benign strictures of the lower esophagus, 382
- Esophagus and the cardia of the stomach, transthoracic resection of lesions of the lower portion of, 279
 - , dilated ampulla and diaphragmatic hernia, 270
 - , esophagobronchial fistula through an esophageal diverticulum, 499
 - , idiopathic dilatation of, 151
 - , observations concerning Salzer method of treatment of lye burns of, 498
- , paraesophageal hiatal hernia, 699
- , radiological diagnosis of certain diseases of, 699
- , regional, 142
- , transthoracic esophagogastronomy for benign strictures of, 382

- Fluorescein, use in determining viability of strangulated intestine, 271
- Folic acid, activity of, as an antipernicious anemia substance, 277
- , synthetic, anti-anemic, properties of, 277
- , — L. casei factor, treatment of sprue with, 273
- , treatment of tropical sprue with, 504
- Fumaric acid salts as hydrogogue cathartics, 273

- Gall bladder, see also biliary tract
 - , advanced carcinoma of the extrahepatic bile ducts: Cholangiocholecystocholecystectomy, 146
 - , diverticula (Luschka's crypts) of, 275
 - , — of the colon versus gallstones, 386
 - , etiology of gallstones, 145
 - , hydrops of, 591
 - , management of post-operative choledocholithiasis, use of solution G, 145
 - , papilloma of, 703
 - , penicillin in acute cholecystitis, 592
 - , studies on serum phosphatase in relation to experimental biliary obstruction in rabbits, 592
 - , traumatic rupture of, case reports and notes on choleperitoneum, 388
- Gastrectomy, partial, and vagotomy, effect of, on gastric acidity, 710
 - , subtotal, in the treatment of ulcer, 595
 - , —, the so-called "dumping syndrome" after, 595
 - , total transthoracic, multiple carcinomas of the stomach, 700
- Gastroenterostomy, operation of ligature of the arteries of the stomach to relieve hyperacidity and to prevent recurrent ulceration after, 140
 - , posterior, for duodenal ulcer, gastric retention after, prevention and treatment, 594
- Gastroscopy and roentgenology, studies of gastric mucosa in infectious hepatitis, 591
 - , clinical value of, 501

- Gastroscopy and roentgenology, evaluation of criteria useful in the differentiation of benign and malignant lesions of the stomach, 585
- , roentgenology and pathology, correlation of findings in diseases of the stomach, 499
- , study of gastric lesions by means of biopsy specimens removed endoscopically, 382
- Genito-urinary symptoms of anorectal disease, 509
- Glucose tolerance test in patients with jaundice, 597
- — —, intravenous, in liver disease, 704
- Hemicolectomy, Lahey, right, an aid in the post-operative management of temporary ileal fistula after, 148
- Hepatitis, see also Liver
- , acute epidemic, pathological aspects of, especially early stages, 590
- , —, studies of the Van den Berg reaction, 389
- , infectious, gastric mucosa in; roentgenologic and gastroscopic studies, 591
- , —, liver function in, gauged by hippuric acid synthesis tests, 276
- , —, pre-icteric stage of, value of biochemical findings in diagnosis of, 592
- , —, transient non-specific Wasserman and Kahn reactions in a case of, 506
- , —, transmission by feces and urine, 387
- , virus, infectious, demonstration of in pre-symptomatic period after transfer by transfusion, 505
- , —, —, parenterally introduced, elimination in human feces, 505
- Hernia, diaphragmatic and dilated esophageal ampulla, 270
- , intra-abdominal, acute intestinal obstruction, 273
- , para-esophageal hiatal, 699
- Hippuric acid synthesis tests, gauging liver function in infectious hepatitis, 276
- — — — of liver function, some difficulties in interpretation, 593
- Histaminase preparations, action of in the Heidenhain dog, 151
- Histamine, blood, level in experimental burns, 507
- , experimental hyperplasia of the stomach mucosa, 148
- Hookworm disease, a small intestinal study, 272
- Hyperuricemia in gastric cancer, 700
- Ileostomy and colectomy in chronic ulcerative colitis, 143
- Ileum and jejunum, diverticulum of, 589
- Intestine, absorption from, influence of induced changes in blood plasma osmotic activity on, 149
- , — of fat, anomalies of determination and significance of fecal fat, 710
- , case of left-sided appendicitis, 144
- , an aid in the post-operative management of temporary ileal fistula after the Lahey right hemicolectomy, 148
- , chronic hypertrophic ileocecal tuberculosis and its relation to regional ileitis, 143
- , chronic nonspecific regional enteritis, 273
- , clinical aspects of the bowel obstruction problem, 503
- , complete duodenal obstruction in the newborn, 589
- , congenital duodenal obstruction, 588
- , detecting the protozoa of saline-iron-hematoxylin solution for wet smears, 391
- , diverticulitis of the veriform appendix, 142
- , diverticulum of the jejunum and ileum, 589
- , intra-abdominal hernia with acute intestinal obstruction, 273
- , intussusception-diagnosis and treatment, 141
- , left-sided appendicitis, in a dextrocardiac patient, 502
- , lipodystrophy of, 142
- , management of chronic constipation, 386
- , mechanical obstruction following war wounds of the abdomen, 510
- , Meckel's diverticulum with report of a case of intussusception due to its invagination, 503
- , observations on treatment of tropical sprue with folic acid, 504
- , obstruction of, 708
- of dogs, effects of temperature on the experimental production of ulcers in, 278
- , penicillin therapy in ulcerative colitis, 589
- , regional enteritis, 142
- , resection of rectum with reconstruction of canal through the perineal approach, 509
- , *Salmonella* gram-negative bacilli, 144
- , significance of chronic enteritis, 386
- , treatment of some common infections of the bowel with sulfonamide drugs, 702
- , unusual types of appendicitis, 587
- , volvulus and gangrene of the sigmoid complicated by Manson's schistosomiasis, 588
- , — of megacolon reduced during barium enema examination, 143
- , large, amebic colitis with special reference to perforation, 272

- , —, anastomosis of, preliminary report of a method for the prevention of leakage of, 595
- , —, carcinoma complicating ulcerative colitis, 141
- , —, — of the colon, 140
- , —, — and rectum, 503
- , —, clinical significance of deformity of the cecum in amebiasis, 384
- , —, closure of colostomies, 708
- , —, (colon duplex), duplication of, 509
- , —, congenital or hereditary polyposis of the colon, 142
- , —, diagnosis and management of ulcerative colitis, 501
- , —, — of acute appendicitis in the presence of diarrhea, 701
- , —, — of amebiasis, 504
- , —, diverticula of the colon versus gallstones, 386
- , —, diverticulitis of the colon, 709
- , —, fumaric acid salts as hydrogogue cathartics, 273
- , —, ileostomy and colectomy in chronic ulcerative colitis, 143
- , —, improved method for extraperitoneal closure of colostomy, 148
- , —, isolation and testing of fecal streptococci, 598
- , —, modern concept of congenital megacolon, 385
- , —, one stage "open" resection of lesions of the left colon without complimentary colostomy, 141
- , —, peritonitis following malignant obstruction of sigmoid and free perforation, 701
- , —, proctoscopy and barium colon study in the diagnosis of rectal conditions, 708
- , —, primary resection of malignant lesions of, 590
- , —, redundancy of colon, 502
- , —, roentgen examination in congenital defects in infants, 270
- , —, routine examination of stool for parasites, 712
- , —, sulfonamides in bacillary dysentery, 383
- , —, surgical treatment of dysenteric lesions of, 385
- , —, treatment of amebiasis with special reference to chronic amebic dysentery, 384
- , —, — sprue with synthetic L. casei factor (folic acid, vitamin M.), 273
- , —, — ulcerative colitis with nisulfadine and nisulfazole, 502
- , —, veriform appendix and urinary bladder, duplication of, 281
- , —, small, acute obstruction of, 386
- , — and cecum of inbred strains of mice, anomalies in, 711
- , —, diagnosis of disorders of, 386
- , —, hookworm disease, 272
- , —, inhibitory effect of mineral oil on experimental production of ulcers, 278
- , —, lipodystrophy, 271
- , —, lymphoblastoma of, 701
- , —, obstruction of, early diagnosis and management of, 702
- , —, Paneth cells in carcinomas of, in mouse and rat, 148
- , —, spontaneous rupture of lower colon with evisceration of, through anal orifice, 144
- , —, sprue in India, 385
- , —, roentgen, study of, 384
- , —, strangulated, fluorescein use in determining viability of, 271
- Intussusception, diagnosis and treatent, 141
- , Meckel's diverticulum with report of a case of, due to its invagination, 503

- Jaundice, see also liver
- congenital obliteration of bile ducts and icterus gravis neonatorum, 387
- , familial acholuric, and pernicious anemia, a note of the differential diagnosis of, 598
- , glucose tolerance in patients with, 597
- , investigation of the phosphatase activity in serum and organs after ligation of the common bile duct in dogs, 703
- , obstructive and hemolytic, studies of the Van den Berg reaction, 389
- , studies of serum phosphatase activity in relation to experimental biliary obstruction in rabbits, 145, 592
- Jejunum and ileum, diverticulum of, 589

- Leiomyosarcoma of the stomach, 586
- Lipodystrophy, intestinal, 142, 271
- Lipoma, submucous of the stomach, 586
- Liver, carbon tetrachloride injury of, protective action of certain compounds, 275
- , choleretic action of the allyl ester of cinchophen, 711
- , comparison of the results obtained with the Hangar cephalin-cholesterol flocculation test and the Maclagan thymol turbidity tests in patients with liver disease, 274
- , cystic disease of, 389

- Liver, degalol and decholin, choleric action of, in chronic biliary fistula dogs, 275
- , demonstration of infectious hepatitis virus in presymptomatic period after transfer by transfusion, 505
- disease, intravenous glucose tolerance test in, 704
- —, therapy of, 146
- , effect of methionine supplements on hepatic injury produced by carbon tetrachloride, 505
- , elimination in human feces of infectious hepatitis virus parenterally introduced, 505
- , functional and fatty changes in during chronic vitamin B complex deficiency, 596
- , functional impairment in therapeutic malaria with particular reference to unsuccessful use of methionine as a protective agent, 387
- function, hippuric acid synthesis test of, some difficulties in interpretation, 593
- — in healthy soldiers, normal values for certain tests of, 590
- — — infective hepatitis gauged by hippuric acid synthesis tests, 276
- , gastric mucosa in infectious hepatitis; roentgenologic and gastroscopic studies, 591
- , glucose tolerance in patients with jaundice, 597
- , infective hepatitis, transmission by feces and urine, 387
- , investigations of the phosphatase activity in serum and organs after ligation of the common bile duct in dogs, 703
- , metastatic, disease of, and alkaline phosphatase, 704
- , Laennec's cirrhosis of, the plasma volume in, 592
- , pancreatic juice and bile of the dog, the elimination of administered cobalt in as measured with its radioactive isotopes, 391
- , pathologic aspects of acute epidemic hepatitis with especial reference to early stages, 590
- , Pre-icteric stage of infective hepatitis, value of biochemical findings in diagnosis, 592
- , roentgen findings in amebic disease of, 388
- , subacute necrosis of, without icterus, 591
- , transient non-specific Wasserman and Kahn reactions in a case of infective hepatitis, 506
- , significance of fatty infiltration in the development of hepatic cirrhosis due to choline deficiency, 505
- , studies of the Van den Berg reaction, 389
- , cirrhosis of, experimental dietary, thiouracil in the prevention of, 147
- , — —, response to an intensive combined therapy, 703
- , — —, treatment of experimental, 276
- , — —, use of salt-poor concentrated human serum albumin solution in the treatment of, 705
- Lymphoblastoma of the small intestine, 701
- Lymphosarcoma of the stomach, 140
- Malaria, therapeutic, liver functional impairment in, with particular reference to the unsuccessful use of methionine as protective agent, 387
- Meckel's diverticulum, with report of a case of intussusception due to its invagination, 503
- Megacolon, congenital, modern concept of, 385
- , volvulus of, reduced during barium enema examination, 143
- Metabolism, abnormalities in obesity, 281
- . Thiamine balance, normal requirements of vitamin B, and the role of fecal thiamine in human nutrition, 711
- . Thiamine, studies of in man, 710
- Methionine, as an unsuccessful agent in liver functional impairment in therapeutic malaria, 387
- supplements, effect of on hepatic injury produced by carbon tetrachloride, 505
- Mononucleosis, infectious. Pre-icteric stage of infective hepatitis, value of biochemical findings in diagnosis, 592
- Nisulfadine and nisulfazole, treatment of ulcerative colitis with, 502
- Nutrition, etiology of beriberi and epidemic dropsy, 710
- , human, normal requirements of vitamin B, and the role of fecal thiamine in, 711
- . Thiamine and pyrimidine excretion with special reference to relationship between injected and excreted thiamine in normal and abnormal subjects, 710
- Obesity, metabolic abnormalities in, 281
- Obstruction of bowel, clinical aspects of, 503
- Pancreas, anatomic study of pancreatic and extrahepatic biliary system, 276
- , annular, causing duodenal obstruction, 593
- , cyst of, roentgen diagnosis of, 705
- , innervation of, 281

- , insufficiency of, in early life, roentgen changes associated with, 594
- , number and relative concentrations of protein constituents of canine pancreatic juice as determined by electrophoresis, 280
- , on the activation of lipase by calcium chloride at varying pH., 150
- , simulating carcinosarcoma, cancerous cyst of the tail of, 593
- Pancreatectomy, total, 4 successful cases and a report on metabolic observations, 389
- Pancreatic juice and bile of the dog, the elimination of administered cobalt in, as measured with its radioactive isotopes, 391
- Pancreatitis*, acute, 506
- , — hemorrhagic, relation of cholelithiasis to, 389
- Paneth cells in carcinomas of the small intestine in a mouse and in a rat, 148
- Papilloma of the gall bladder, 703
- Parasites of stool, large scale routine examination of, 712
- Parotid gland, cylindroma type of adenocarcinoma, 499
- Penicillin, absorption of, from the nose and the alimentary canal, 151
- and streptomycin, excretion and concentration of in the abnormal biliary tract, 506
- in acute cholecystitis, 592
- therapy in ulcerative colitis, 589
- Peritonitis following malignant obstruction of sigmoid and free perforation, 701
- Phosphatase activity in serum and organs after ligation of the common bile duct in dogs, 703
- , alkaline, and metastatic liver disease, 704
- , serum, studies on relation to experimental biliary obstruction in rabbits, 145, 592
- Plasma, fractionation, human, chemical, clinical and immunological studies on the products of, 705
- Polyposis of the colon, congenital or hereditary, 142
- Proctology, genito-urinary symptoms of anorectal disease, 509
- , resection of the rectum with reconstruction of canal through the perineal approach, 509
- Proctoscopy and barium colon study in the diagnosis of rectal conditions, 708
- Psychosomatic medicine, disorders of the upper gastrointestinal tract in combat personnel, 282
- Pyloric obstruction, importance of urinary chloride determinations in treatment of patients having, 597
- Pyrimidine and thiamine excretion, 710
- Radiology and gastroscopy, studies of gastric mucosa in infectious hepatitis, 591
- , chronic nonspecific regional enteritis, 273
- , clinical significance of deformity of the cecum in amebiasis, 384
- , congenital duodenal obstruction, 588
- , correlation of gastroscopic, roentgenologic and pathologic findings in diseases of the stomach, 499
- , diagnosis of certain diseases of esophagus, 699
- , — diagnosis of pancreatic cyst, 705
- , diverticulum of the jejunum and ileum, 589
- , duplication of the entire large intestine (colon duplex), 509
- , esophagobronchial fistula through an esophageal diverticulum, 499
- , evaluation of the criteria useful in the differentiation of benign and malignant lesions of the stomach, 585
- , examination in congenital intestinal obstructive defects in infants, 270
- , findings in amebic disease of the liver, 388
- , hookworm disease, a small-intestinal study, 272
- , Roentgen changes associated with pancreatic insufficiency in early life, 594
- , Study of the small intestine, 384
- , supine projection in the diagnosis of lesions of the corpus and posterior wall of the stomach, 587
- , unusual gastrointestinal roentgenology, 283
- , volvulus of megacolon reduced during barium enema examination, 143
- Rectum, resection of, with reconstruction of canal through the perineal approach, 509
- Roentgenology, see Radiology
- Salmonella, gram-negative bacilli, 144
- , treatment of some common infections of the bowel with sulfonamide drugs, 702
- Salzer treatment of lye burns of esophagus, 498
- Scleroderma with involvement of the viscera: report of a case, 149
- Schistosomiasis, Manson's volvulus and gangrene of the sigmoid complicated by, 588
- Secretion, gastric HCl, influence of anoxia on, 596
- Skin, scleroderma with involvement of the viscera, 149
- Solution G, management of post-operative choledocholithiasis, 145

- Sprue, tropical, treatment of, with folic acid, 504
—, in India, 385
—, treatment of, with synthetic *L. casei* factor, 273
Stomach, acid-fast organisms in gastric resting juice, 151
—, action of histaminase preparations in the Heidenhain dog, 151
— and other viscera, direct irradiation of cancer of, 383
—, blood group substances from human gastric contents, 392
—, brucellosis and peptic ulcer, 390
—, calcium and potassium content of secretions from noncancerous and cancerous stomachs, 500
—, carcinoma of, ten year survey made in a general hospital, 699
—, cardia of, and esophagus, transthoracic resection of lesions of, 279
—, clinical evaluation of the laboratory tests of, 383
—, — value of gastroscopy, 501
—, correlation of gastroscopic, roentgenologic and pathologic findings in diseases of, 499
—, disappearance of peptic ulcer after feeding of normal human gastric juice, 147
—, diverticula of, 382
—, effect of vagotomy and partial gastrectomy on gastric acidity, 710
—, electrical impedance properties of surviving gastric mucosa of the frog, 280
—, etiology and treatment of peptic ulcer, 507
—, experimental hyperplasia of the stomach mucosa, 148
—, evaluation of criteria useful in the differentiation of benign and malignant lesions, 585
—, extramedullary plasma cell tumor, 585
—, gastric retention after posterior gastroenterostomy for duodenal ulcer, prevention and treatment, 594
—, gastroduodenal invagination due to a submucous lipoma of, 586
—, — ulcer, following cutaneous burns, 390
—, hyperuricemia in gastric cancer, 700
—, importance of urinary chloride determinations in treatment of patients having pyloric obstruction, 597
—, influence of anoxia on the gastric HCl secretion, 596
—, leiomyosarcoma of, 586
—, lymphosarcoma of, 140
—, method for bio-assay of extracts which inhibit gastric secretion, 596
—, multiple carcinomas of, 700
—, perforated peptic ulcer, 507
—, presence of a gastric secretory excitant in the human gastric and duodenal mucosa, 150
—, prevention of induced peptic ulcer in dogs by feeding a hog stomach preparation, 148
—, problems of peptic ulcer in the armed forces and in the returned soldiers, 707
—, psychogenic disorders of the upper gastrointestinal tract in combat personnel, 282
—, operation of ligation of the arteries of the stomach to relieve hyperacidity and to prevent recurrent ulceration after gastroenterostomy, 140
—, peptic ulcer among soldiers in the Mediterranean theatre of operations, 508
—, recrudescence of gastro-duodenal ulcer and alimentation during the war period, 706
—, review of errors in diagnosis of gastric carcinoma, 383
—, safety factor in gastric resection, 709
—, small ulcerating lesions of, 700
—, study of gastric lesions by means of biopsy specimens removed endoscopically, 382
—, subtotal gastrectomy in the treatment of ulcer, 595
—, — —, the so-called "dumping syndrome" after, 595
—, submucosal lipomas of, review of literature and report of case associated with carcinoma, 500
—, supine projection in the diagnosis of lesions of the corpus and posterior walls, 587
—, surgery in treatment of bleeding peptic ulcer, 708
—, surgical treatment of chronic duodenal ulcer, 707
—, thoracic, gastric cyst of, 586
—, unusual in gastrointestinal roentgenology, 283
—, vagotomy for gastroduodenal ulcer, 390
Streptococci, fecal, isolation and testing of, 598
Streptomycin and penicillin, excretion and concentration of in the normal biliary tract 506
Sulfonamides in bacillary dysentery, 383
—, local use of sulfanilamide in the treatment of acute appendicitis, 142
—, treatment of some common infections of the bowel with sulfonamide drugs, 702

- Surgery, aid in post-operative management of temporary ileal fistula after the Lahey right hemicolectomy, 148
- , closure of colostomies, 708
- , congenital cystic dilatation of the common bile duct, 388
- , cystic disease of the liver, 389
- , deaths from surgical diseases of the biliary tract, 591
- , diverticulitis of the colon, 709
- , emergencies of the alimentary tract of the newborn, 282
- , improved method for extra-peritoneal closure of colostomy, 148
- , in intestinal obstruction, 708
- , multiple carcinomas of the stomach, 700
- , preliminary report of a method for the prevention of leakage of intestinal anastomosis, 595
- , primary anastomosis in carcinoma of the colon, 279
- , radical resections of advanced intra-abdominal cancer, 391
- , regional enteritis, 142
- , safety factor in gastric resection, 709
- , the so-called "dumping syndrome" after sub-total gastrectomy, 595
- , transthoracic resection of the lower portion of the esophagus and the cardia of the stomach, 279
- , treatment of bleeding peptic ulcer, 708
- , treatment of chronic duodenal ulcer, 707
- , treatment of dysenteric lesions of the bowel, 385
- , vagotomy for gastro-duodenal ulcer, 390
- Thiamine, metabolism studies of in man, 710
- , outbreak of beriberi and etiology of beriberi and epidemic dropsy, 710
- Thiouracil in the prevention of experimental dietary cirrhosis of liver, 147
- Thymol, Machagan, turbidity test and the Hangar cephalin-cholesterol flocculation test in patients with liver disease, 274
- Tuberculosis, acid fast organisms in gastric resting juice, 151
- , chronic hypertrophic ileocaecal, and its relation to regional ileitis, 143
- Ulcer, blood histamine level in experimental burns, 507
- , experimental, prevention of, by feeding a hog stomach preparation, 148
- , inhibitory effect of mineral oil on the experimental production of ulcer, 278
- , nutritional effects on the gastric mucosa of the rat. I. Lesions of the antrum, 278
- , nutritional effects on the gastric mucosa of the rat. II. Lesions of the fundus and rumen, 278
- , perforated peptic, 507
- , subtotal gastrectomy in the treatment of, 595
- , duodenal, gastric retention after posterior gastroenterostomy for; prevention and treatment, 594
- , —, importance of urinary chloride determinations in treatment of patients having pyloric obstruction, 597
- , chronic duodenal, surgical treatment of, 707
- , gastro-duodenal, and cutaneous burns, 390
- , —, alimentation during the war period, 706
- , —, vagotomy for, 390
- , intestinal, effect of bile salts on the experimental production of ulcer in dog, 279
- , —, effects of temperature on the experimental production of, in dogs, 278
- , peptic, among soldiers, 508
- , peptic and brucellosis, 390
- , —, bleeding, surgical treatment of, 708
- , —, disappearance after feedings of normal human gastric juice, 147
- , —, etiology and treatment of, 507
- , —, hyperinsulinism as a factor in, 278
- , —, operation of ligation of the arteries of the stomach to relieve hyperacidity and to prevent recurrent ulceration after gastro-enterostomy, 140
- , —, problems of in the armed forces and in the returned soldiers, 707
- , —, transdiaphragmatic resection of the vagus nerves for, 508
- Ulcerating lesions of the stomach, 700
- Urogastrone, the relation of endocrine glands to the gastric secretory depressant in, 150
- Vagotomy and partial gastrectomy, effect of, on gastric acidity, 710
- for gastroduodenal ulcer, 390
- for peptic ulcer, 508
- Vitallium tubes, reconstruction of the common duct with, 146
- Vitamin B complex, and amino acids, role of the coenzymes of, in muscle metabolism and balanced nutrition, 597
- , —, functional and fatty changes in liver during deficiency, 596

- Vitamin B complex, normal requirement of and the role of fecal thiamine in human nutrition, 711
- Vitamin M, folic acid, synthetic *L. casei* factor, treatment of sprue with, 273
- War Medicine, mechanical intestinal obstruction following war wounds of the abdomen, 510
- , normal values for certain tests of liver function in healthy soldiers, 590
- , peptic ulcer among soldiers in the Mediterranean theatre of operations, 508
- , problems of peptic ulcer in the armed forces and in the returned soldiers, 707
- , psychogenic disorders of the upper gastrointestinal tract in combat personnel, 282
- , recrudescence of gastroduodenal ulcer and alimentation during the war period, 706
- , surgical treatment of dysenteric lesions of the bowel, 385
- Wasserman and Kahn reactions, transient non-specific, in a case of infective hepatitis, 506

GASTROENTEROLOGY

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1946

CONTENTS

(Ed.) Signifies Editorial

(Com.) Signifies Comment

No. 1, JULY, 1946

PAGE

Results of Hepatic Tests in Chronic Hepatitis Without Jaundice. John R. Neefe.....	1
A Study of the Time of "Healing" of Peptic Ulcer in a Series of Sixty-Nine Cases of Duodenal and Gastric Craters. George M. Cummins, Jr., M. I. Grossman, and A. C. Ivy.....	20
Nocturnal Gastric Secretion—Part II. Studies on Normal Subjects and Patients with Duo- denal Ulcer. David J. Sandweiss, M. H. F. Friedman, M. H. Sugarman, and H. M. Podolsky.....	38
Complications of Chronic Non-Specific Ulcerative Colitis. William E. Ricketts and Walter Lincoln Palmer.....	55
The Etiology of Ulcerative Colitis: An Analytical Review of the Literature. R. S. Ginsberg, and A. C. Ivy.....	67
Some Results of the Gastric Secretory Response of Patients Having Duodenal Ulcer Noted During the Administration of Benadryl. Robert U. Moersch, Andrew B. Rivers, and Carl G. Morlock.....	91
Clinical Observations on the Use of Benadryl: Its Effect on Histamine-Induced Gastric Acidity in Man. Thomas W. McElin, and Bayard T. Horton.....	100
Separation and Assay of Secretin and Cholecystokinin. Henry Doubilet.....	108
Clinical Pathological Conference. Julian M. Ruffin, and George Margolis.....	118
Clinical Pathological Conference. A. J. Atkinson.....	121
Clinical Pathological Conference. H. M. Pollard.....	126
Frank Howard Lahey, Friedenwald Medalist for 1946, (Ed.). Sara Jordan.....	131
Frank Howard Lahey, Friedenwald Medalist for 1946, (Ed.). A. C. Ivy.....	133
Histamine and Gastric Secretion in Relation to Anti-Histamine Drugs, (Com.). M. I. Gross- man and A. C. Ivy.....	134
Observations on the Healing of Gastric Ulcers, (Com.). H. M. Pollard, William H. Bachrach, and Malcolm Block.....	136
Alteraciones Hepáticas Na Tireotoxicose, (Book Review).....	139
Ambulatory Proctology, (Book Review).....	139
Abstracts.....	140

No. 2, AUGUST, 1946

The President's Address. A. H. Aaron.....	153
Military Gastroenterology—The summing-up. Donald T. Chamberlin.....	162
The Differential Diagnosis of 207 Hospitalized Cases of Peptic Ulcer. Robert C. Kirk.....	168
Correlated Gastroscopic and Psychiatric Studies of Soldiers with Chronic Non-Ulcerative Dys- pepsia. James A. Halsted, I. Richard Schwartz, Samuel R. Rosen, Henry Weinberg, and Stanley M. Wyman.....	177
Clinical Findings in American Soldiers Released from a German Prison Camp. Manfred Kraemer.....	191
Gastrointestinal Bleeding in Hereditary Hemorrhagic Telangiectasia. Historical Review and Case Report with Gastroscopic Findings and Rutin Therapy. Samuel D. Kushlan.....	199
The Effects of B-Dimethylaminoethyl Benzilate Hydrochloride on Intestinal Activity. K. G. Wakim, Clarence E. Powell, and K. K. Chen.....	213
The Effect of Glucose on the Motility of the Stomach and Small Intestine. Edward J. Van Liere, David W. Northup, and J. Clifford Stickney.....	218
The Effect of Pilocarpine on Mucus Secretion by the Pyloric Mucosa. J. S. Ivy.....	224

	PAGE
Hematemesis Associated with Gastric Arteriosclerosis; A Review of the Literature with a Case Report. William Frank.....	231
Puzzling "Nervous Storms" Due to Food Allergy. (Case Report.) Walter C. Alvarez.....	241
Clinical Pathological Conference. A. J. Atkinson.....	243
Dr. Aaron's Presidential Address, (Ed.). W. C. Alvarez.....	249
The Use of Elimination Diets and Food Diaries in the Diagnosis of Food Allergy, (Ed.). W. C. Alvarez.....	249
Gastric Tumors Produced in Insects by Cutting the Nerve to the Stomach, (Ed.). W. C. Alvarez.....	252
Supradiaphragmatic Vagotomy for Ulcer, (Com.). H. M. Pollard, William H. Bachrach, and Malcolm Block.....	254
Recent Advances in Cytochemistry, (Com.). Paul Klempner.....	256
Books—War Victims, (Com.). K. R. Shaffer.....	259
Report of Advisory Committee on Gastroenterology of the American Board of Internal Medicine.....	261
Gastroenterology, (Book Review).....	264
Medical Diagnosis, (Book Review).....	264
The Person in the Body, (Book Review).....	267
Clement R. Jones, Obituary. A. A. Aaron.....	267
Alexander Berkely Moore, Obituary. William Earl Clark.....	268
Abstracts.....	270

No. 3, SEPTEMBER, 1946

Gastroscopy and its Relationship to Roentgenology in the Diagnosis of Carcinoma of the Stomach. Herman J. Moersch, and B. R. Kirklin.....	285
Backache Due to Intra-Abdominal Disease. Henry J. Tumen and Joseph C. Yaskin.....	294
A Note on Bacteriological and Parasitic Studies of the Intestinal Contents of Patients with Sprue. Fernando Milanes, Arturo Curbelo, Aureliano Rodriguez, Pedro Kouri and Tom D. Spies.....	306
Peptic Ulcer of the Esophagus—Report of a Patient with 10 Year Follow-up. D. R. Morton, and A. Brunschwig.....	314
Hematemesis: A Study of Underlying Causes. Harold Lincoln Thompson, Joseph M. Oyster, John B. Heid, and Frank M. Morgan.....	320
Gastric Secretion in Duodenal Ulcer in Remission—Response to the Caffeine Test Meal. V. H. Musick, H. T. Avey, H. C. Hopps, and A. A. Hellbaum.....	332
Vascular Changes in the Mucosa in Experimental Nutritional Gastritis. Benjamin N. Berg, Theodore F. Zucker, and Lois M. Zucker.....	340
A Case of Lung Tumor with Prominent Abdominal Changes, (Case Report). Leon Schiff.....	355
Acute Enterocolitis and Death Resulting from a Markedly Hypertonic Enema, (Case Report). Stuart Lindsay.....	364
The Approaching Synthesis of Penicillin, (Ed.). W. C. Alvarez.....	371
A Cause of Nausea, (Ed.). W. C. Alvarez.....	371
Studies of Peptic Ulcer Among Soldiers in the Mediterranean Theater of Operations, (Ed.). W. C. Alvarez.....	372
In Memoriam: The Carbonic Anhydrase Theory of Gastric Acid Secretion, (Com.). Horace W. Davenport.....	374
Concerning the Carbonic Anhydrase Theory of HCl Formation, (Com.). F. Hollander.....	375
The Anoxia Test as an Aid in the Diagnosis of Coronary Insufficiency, (Com.). Raymond D. Pruitt.....	376
Cornell Conferences on Therapy—Vol. 1, (Book Review).....	379
Tratamiento Dietetico de Los Gastrectomizados, (Book Review).....	380
Surface Active Agents, (Book Review).....	380

	PAGE
The Vitamins in Medicine, (Book Review).....	380
Abstracts.....	382

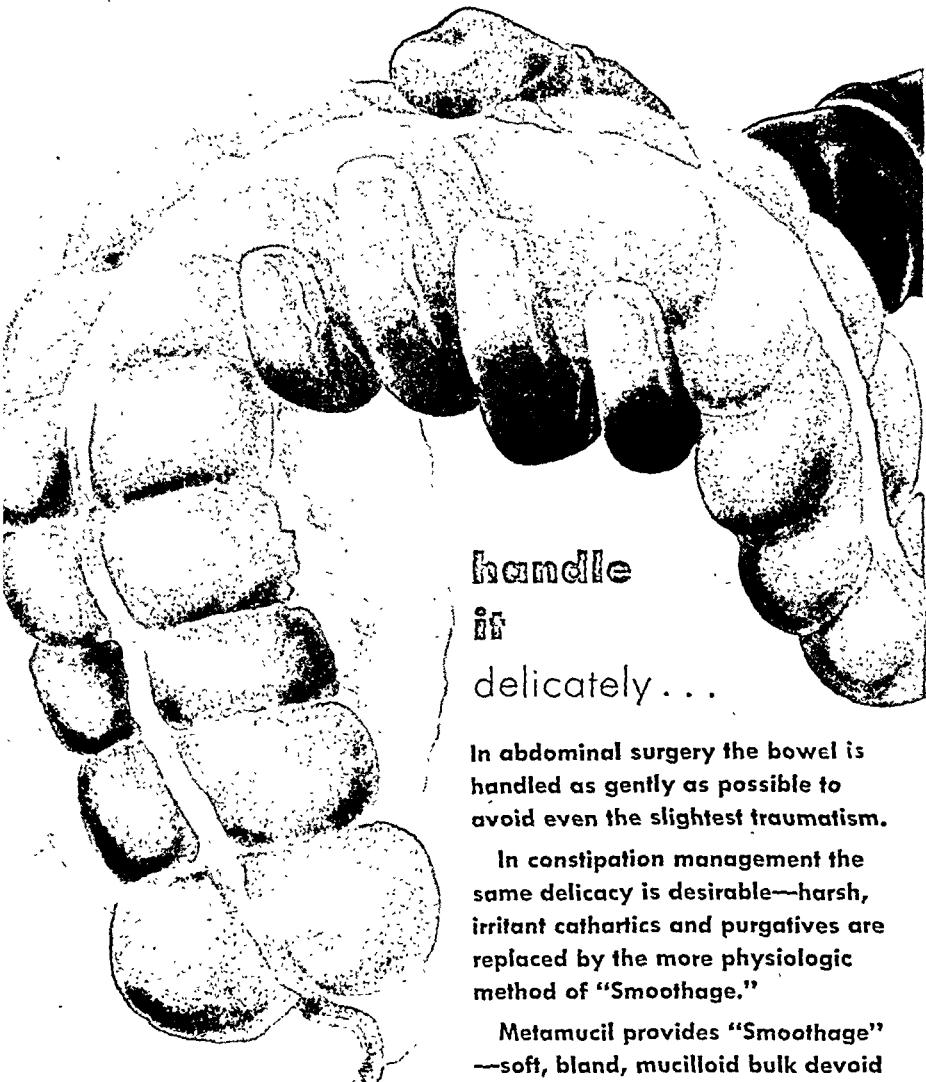
No. 4, OCTOBER, 1946

Laboratory Aids in the Diagnosis and Management of Infectious (Epidemic) Hepatitis. John R. Neefe, and John G. Reinhold.....	393
The Treatment of Postoperative Biliary Dyskinesia. Ralph Colp.....	414
Nutritional Deficiency as a Probable Cause of Hepatic Damage in Repatriated Prisoners of War. Leo J. Meienberg, and Albert M. Snell.....	430
Amino Acid Alimentation in Gastro-Intestinal Diseases. John H. Remington, John S. Lundy, and J. Arnold Bargen.....	442
The History of Hemorrhage in Peptic Ulcer. S. Allen Wilkinson, and Martin L. Tracey.....	450
The Relationship of Trauma to the Perforation of Peptic Ulcer. Burrill B. Crohn, Milford O. Rouse, and Hubert W. Smith.....	456
Hypertrophic Pyloric Stenosis in the Adult. Martin Vorhaus.....	464
B Vitamins, Intestinal Absorption and Food Utilization. I. Studies in Rats on Diets Deficient in Certain B Vitamins and During Recovery from Such Diets. T. L. Althausen, John J. Eiler, and Mabel Stockholm.....	469
Clinical Pathological Conference. A. J. Atkinson.....	477
Unusual Initial Onset of Ulcerative Colitis With Exsanguinating Bowel Hemorrhage, (Case Report). E. Jobb.....	483
Abdominal Pain Due to Myositis and Fibrosis of the Psoas Muscle, (Ed.). W. C. Alvarez.....	489
Hirsutism in Women, (Ed.). W. C. Alvarez.....	490
Medical Education and Practice in Germany During World War II, (Com.). W. C. Alvarez.....	493
The Recent Decline in the Mortality from Acute Appendicitis, (Com.). W. C. Alvarez.....	494
A New and Hopeful Thought in the Treatment of Cancer, (Com.). W. C. Alvarez.....	494
Mustard Gas as a substitute for Roentgenotherapy, (Com.). W. C. Alvarez.....	495
The Modern Treatment of Diabetes Mellitus, (Book Review).....	496
Roentgen Diagnosis of Diseases of the Gastrointestinal Tract, (Book Review).....	496
Studies in Hypertony and the Prevention of Disease, (Book Review).....	496
Abstracts.....	498

No. 5, NOVEMBER, 1946

Gastrocolic Fistula: A Clinical and Experimental Study. R. John F. Renshaw, Robert M. Kiskadden, and Frederic E. Templeton.....	511
Recurrent Diarrhea Due to Infection with Typhimurium. Abraham Penner.....	522
Bacillary Dysentery. Phillip W. Brown.....	525
Chronic Diarrhea in Military Personnel Returning from the Tropics. Bruce Kenamore.....	528
Dysentery in American Troops in the Middle East. C. Wilmer Wirts, Jr.....	533
Amebic Disease of the Cecum: Clinical and Radiological Aspects. Dwight L. Wilbur, and John D. Camp.....	535
Succinyl Sulfathiazole (Sulfasuxidine) in the Treatment of Chronic Ulcerative Colitis. E. N. Collins, and J. S. Hewlett.....	549
B Vitamins, Intestinal Absorption and Food Utilization. II. Metabolism studies in rats on diets deficient in certain B vitamins and during recovery from such diets. T. L. Althausen, John J. Eiler, and Mabel Stockholm.....	555
Clinical Pathological Conference. H. M. Pollard.....	562
Acute Pancreatitis. Report of a Case Showing Serum Calcium Changes as well as a Grey Turner Sign. William F. Lipp.....	569
Color Changes in the Mucosa of the Colon as Affected by Food and Psychic Stimuli, (Ed.). W. C. Alvarez.....	574

	PAGE
Cholesterol Apparently Protects Against the Development of Certain Arterial Lesions, (Ed.). W. C. Alvarez.....	575
Caffeine and "Peptic" Ulcer, (Com.). J. A. Roth and A. C. Ivy.....	576
Autonomic Nervous System, (Book Review).....	583
Estudo Medico-Cirurgico da Esquistosomiasis De Manson, (Book Review).....	584
The Management of Obesity, (Book Review).....	584
Abstracts.....	585
 No. 6, DECEMBER, 1946	
The Effect of Transthoracic Vagotomy Upon the Clinical Course of Patients With Peptic Ulcer. Julian M. Ruffin, Keith S. Grimson, and R. Cathcart Smith.....	599
The Insulin Test for the Presence of Intact Nerve Fibers After Vagal Operations for Peptic Ulcer. Franklin Hollander.....	607
The Effectiveness of Parenterally Administered "Enterogastrone" in the Prophylaxis of Recurrences of Experimental and Clinical Peptic Ulcer. Harry Greengard, Arthur J. Atkinson, M. I. Grossman, and A. C. Ivy.....	625
Intestinal Parasites in Service Personnel in the South Pacific: with Special Reference to the Incidence and Treatment of Strongyloidiasis. John H. Willard.....	650
Surgery in Acute Pancreatitis. Robert Elman.....	656
Etiology of Cholecystitis. Martin E. Ruhfuss.....	665
Cholecystitis and Cholelithiasis in Identical Twins, (Case Report). James Tesler.....	685
Case Report. Manfred Kraemer.....	687
Vagotomy in the Treatment of Ulcer, (Ed.). Julian Ruffin.....	692
Anorexia Nervosa, A Mental Disease, (Ed.). W. C. Alvarez.....	693
The Virus of Lymphogranuloma Venereum, (Com.). W. C. Alvarez.....	696
A Drug which Doubles the Analgesic Effects of Opium and its Derivatives, (Com.). W. C. Alvarez.....	697
Preventive Medicine and Public Health, (Book Review).....	698
Medical Biochemistry, (Book Review).....	698
Chemistry of Food and Nutrition, (Book Review).....	698
Men Without Guns, (Book Review).....	698
Abstracts.....	699



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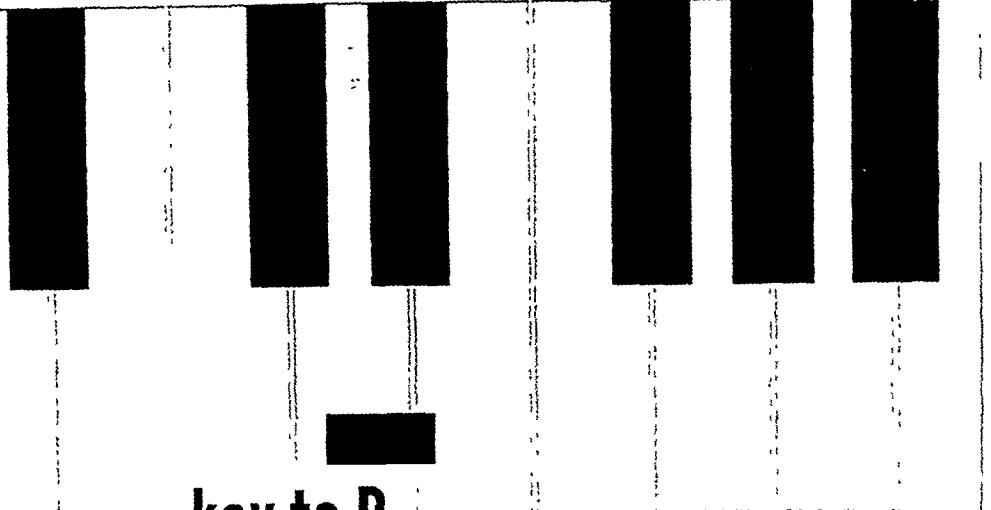
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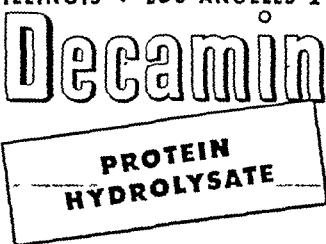
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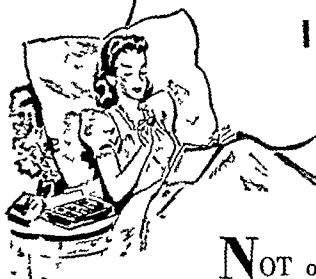
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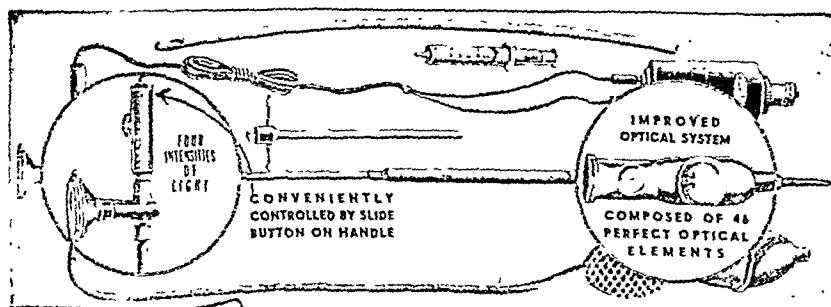
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At the request of the Board of Governors of the American Gastroenterological Association, Dr. Julian M. Ruffin wrote the members of the Association to ascertain those members and institutions which were able to provide a short course or extended graduate study in Gastroenterology. The following have responded.

Those who are interested in obtaining such instruction should write promptly to the person or school of their choice, because in most instances the number of students who can be accommodated is limited.

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INDEX TO ADVERTISERS

PAGE

Abbott Laboratories.....	Cover 3
Armour Laboratories.....	14
Breon & Company, George A.....	11
Brooklyn Scien. Products.....	6
Burton, Parsons & Co.....	31
Camel Cigarettes.....	10
Ciba Pharmaceutical Prod., Inc.....	9
Gerber Products Co.....	7
Harrower Laboratory	25
Hoffmann-LaRoche, Inc.....	32
Lilly, Eli & Co.....	16
Mallinckrodt Chemical Works.....	8
Mead Johnson & Company.....	1
Metro Tec.....	29
Natl. Confectioners Assn.....	27
Paxton, F. H., & Sons, Inc.....	31
Robbins Company, Inc., A. H.....	2
Schering Corp	5
Searle & Company, G. D.....	17
Specific Pharmaceuticals, Inc.....	21
Squibb, E. R. and Sons.....	12
Stearns & Co., Frederick.....	15
Upjohn.....	19
Vico Products Co.....	23
Warner & Co., Inc., Wm. R.....	13
Welin-Sater Co.....	31
Winthrop Chemical Co., Inc.	12, Cover 4
Wyeth, John & Brother, Inc..	Cover 2

